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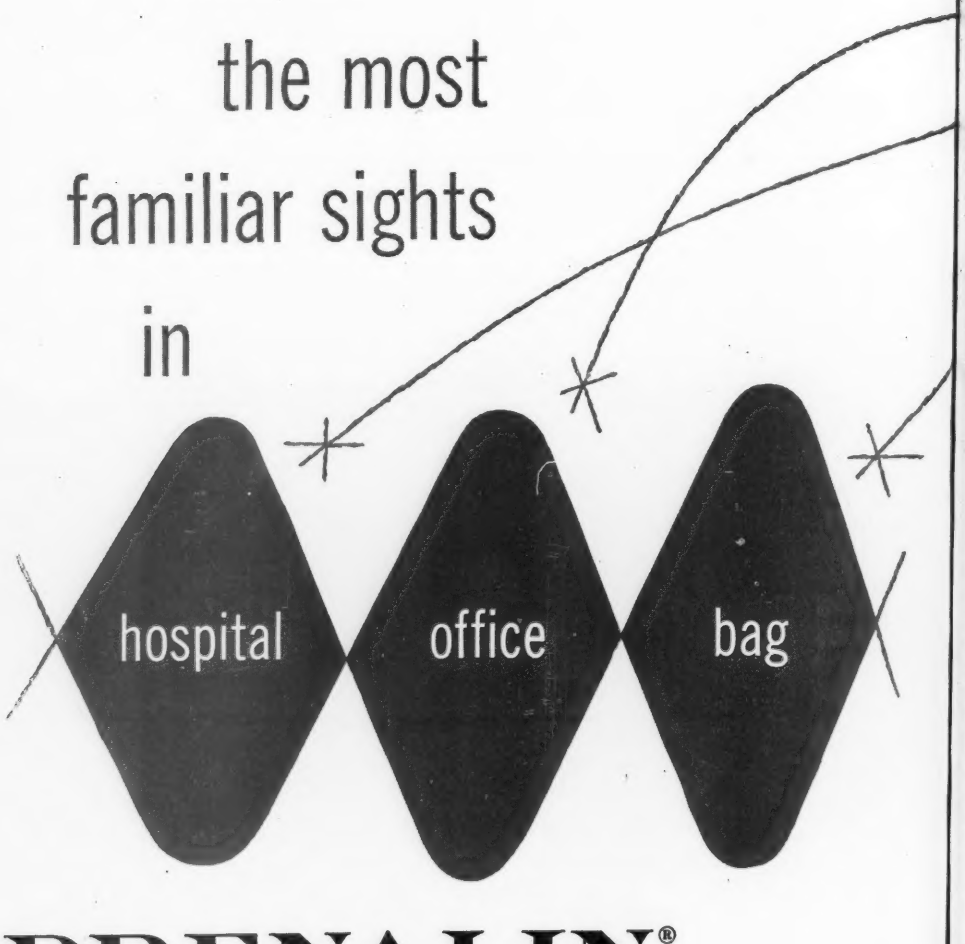

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Volume 247 NOVEMBER 13, 1952 Number 20

HEPATIC HYPOGLYCEMIA*

Its Occurrence in Congestive Heart Failure

SHERMAN M. MELLINKOFF, M.D.,† AND PHILIP A. TUMULTY, M.D.‡

BALTIMORE

MANN'S[1] classic experiments in 1921 first demonstrated that a normal concentration of blood sugar in the hepatectomized animal can be maintained only by a constant infusion of glucose. Spontaneous hypoglycemia has been described in man in cases of obvious liver damage due to cirrhosis, viral hepatitis, chemical poisoning, carcinoma and other processes.[2] Nevertheless, experience with various forms of liver disease at the Johns Hopkins Hospital indicates that episodes of hypoglycemia are frequently overlooked. Furthermore, it is not well appreciated that hepatic hypoglycemia may occur in the absence of other apparent evidence of impaired liver function. Conn et al.[3] first made this important observation in 6 patients with cholangitis. Hepatic hypoglycemia is often overlooked as an explanation for mental peculiarities, convulsions or coma. The fact that such oversight precludes the simple and effective treatment employed so long ago by Mann, is emphasized by experience with 20 patients with hepatic hypoglycemia recently seen at the Johns Hopkins Hospital. These 20 cases are briefly presented to emphasize the fact that hepatic hypoglycemia is not uncommon and may appear in a variety of circumstances, sometimes without other overt indications of extensive liver disease.

CASE REPORTS

CASE 1. D. B. (J.H.H. 265370), a 27-year-old Negress, became anorexic and jaundiced 4 months after receiving several blood transfusions in the treatment of an abdominal stab wound. Physical examination was not remarkable except for jaundice. The laboratory studies were noteworthy only in the findings consistent with the diagnosis of homologous serum jaundice: +++ cephalin-flocculation test; thymol turbidity of 23 units; alkaline phosphatase of 7.2 Bodansky units; and a serum bilirubin of 11.8 mg. per 100 cc. Three days after admission to the hospital, the patient became drowsy, incontinent of urine and combative, and did not recognize her friends. Some observers thought schizophrenia had developed. When the blood sugar was found to be 44 mg. per 100 cc., glucose was given parenterally. Immediately, the patient became rational, remaining so throughout an uneventful recovery from the hepatitis. Subsequent blood sugar determinations were always above 70 mg. per 100 cc.

Except for the episode of disordered behavior, this patient was no more severely ill than many others with hepatitis, nor were the usual chemical indications of liver disease remarkable.

CASE 2. J. P. (J.H.H. 181318), a 65-year-old Negress, experienced chills and fever after dilatation of a ureteral stricture and was admitted to the gynecologic service. For many years she had been treated for chronic pyelonephritis and mild diabetes mellitus. She was known to be a chronic alcoholic; and while receiving her customary 10 units of protamine zinc insulin daily she had several insulin reactions on the ward. The drug was therefore discontinued. Fever disappeared with the administration of Gantrisin and intravenous injection of fluids. Forty-eight hours after all insulin had been discontinued, the fasting blood sugar was 138 mg. per 100 cc., and the patient was quite rational. At 8 p.m., having received approximately 85 gm. of sugar intravenously during the day, she lapsed into profound coma; she lay motionless and was drenched with perspiration. The only other striking physical finding was a hard liver edge 2 fingerbreadths below the right costal margin. Blood was drawn for sugar determination, and 40 cc. of 50 per cent glucose was rapidly injected. The patient immediately awakened, and the blood sugar was subsequently reported to be 8 mg. per 100 cc. Blood chemical studies were as follows: serum bilirubin, less than 0.8 mg. per 100 cc.; alkaline phosphatase, 6.4 Bodansky units; cephalin flocculation, ++; thymol turbidity, greater than 31 units; prothrombin time, 40 per cent of normal; and nonprotein nitrogen, 90 mg. per 100 cc. Careful attention was paid to the intravenous administration of glucose; the patient never again became hypoglycemic, but she eventually died in uremia. Autopsy disclosed chronic pyelonephritis, Kimmelstiel–Wilson lesions in the kidneys, generalized and coronary arteriosclerosis, encephalomalacia and moderately advanced Laënnec's cirrhosis of the liver. The pancreas contained an occasional hyalinized islet and numerous areas of atrophy and focal scarring secondary to squamous metaplasia of the pancreatic ducts, but no islet cell-adenoma or hyperplasia.

It is true that this patient had received insulin prior to the hypoglycemic coma, but forty-eight hours had elapsed since the last injection of insulin, when only 10 units were given, and the morning before she lapsed into coma the fasting blood sugar was 138 mg. per 100 cc. Autopsy gave no explanation for the hypoglycemia other than the liver disease, and although the cirrhosis was moderately severe and involved the entire organ, it had not previously

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caused any clinical difficulty, nor was the patient jaundiced at any time.

CASE 3. B. E. (J.H.H. 535946), a 38-year-old woman, had an 18-month history of a peculiar form of heart failure manifested chiefly by dyspnea and spells of weakness and syncope. She presented signs of congestive heart failure and mental confusion. The day after admission she lapsed into coma. The blood sugar at that time was 23 mg. per 100 cc., and after the administration of 50 cc. of 50 per cent glucose intravenously she roused transiently, but subsequently died in shock. The following liver-function tests were reported: bromsulfalein retention, 16 per cent in 55 minutes; serum bilirubin, 0.5 mg. per 100 cc.; thymol turbidity, 4.5 units; serum albumin, 3.6 gm. per 100 cc.; and serum globulin, 3.4 gm. per 100 cc. The striking finding at autopsy was a myxoma of the left auricle. There was also passive congestion of the viscera, including the liver, and the type of central hepatic necrosis often found in patients dying of heart failure.

Cerebral anoxemia of varying degree is a frequent occurrence in congestive heart failure, and is commonly believed to account for any alterations of consciousness. This case demonstrates that hepatic hypoglycemia may be associated with congestion of the liver in heart failure, in the absence of jaundice. One wonders how many patients with "cardiac coma" may be suffering from hypoglycemia while the attention of the physician is focused not upon the liver but upon the heart.

CASE 4. F. H. (J.H.H. 369902), a 70-year-old Negro, was found at operation to have adenocarcinoma of the head of the pancreas, with metastases to the liver and biliary cirrhosis. A cholecystogastrostomy was performed, and the serum bilirubin fell from 17 to 5 mg. per 100 cc. The patient convalesced at home, feeling weak but rational and communicative. One morning he was found by his family in deep coma. An hour later he was brought to the hospital and given 25 gm. of sugar intravenously. He sat up and spoke rationally. A blood sugar determination before the administration of glucose was 6 mg. per 100 cc. The patient ate a fair meal, was able to walk without assistance and, at his request, returned to his home.

Unfortunately, this patient's subsequent course is unknown to us, but the hypoglycemic episode observed re-emphasized the extent to which the blood sugar may fall in a patient whose liver disease is not otherwise incapacitating.

CASE 5. J. L. (J.H.H. 176606), a 71-year-old Negro, had been treated in the Johns Hopkins Hospital on many occasions for congestive heart failure. He also had a peripheral blood picture suggestive of chronic myelogenous leukemia, treated syphilis and a history of alcoholism. He was uncooperative, and his visits to the clinic were sporadic. One morning, having been ambulatory during the previous day, he was found comatose by friends. The blood pressure was unobtainable, and he was completely unresponsive. In addition, he had anasarca, rales at the lung bases and an enlarged liver. Despite the administration of plasma and glucose he soon died. Blood chemical findings before treatment were as follows: nonprotein nitrogen, 44 mg. per 100 cc., blood sugar, 20 mg. per 100 cc.; carbon dioxide combining power, 18.3 milliequiv. per liter; serum chloride, 84 milliequiv. per liter; and serum bilirubin, 2.9 mg. per 100 cc. Autopsy disclosed syphilitic aortitis, myocardial scars, cardiac dilatation, lobular pneumonia, pulmonary edema and myeloid hyperplasia of the bone marrow. The liver showed marked passive congestion, fatty infiltration in the central portions of the lobules and fine scarring suggestive of early cirrhosis.

The cause of this patient's myocardial disease is not clear from the autopsy findings. It is obvious, however, that he had liver damage that was due at least in part to chronic heart failure, and possibly also due to alcoholism. The liver disease, which was the only apparent reason for the hypoglycemia, had never clinically been a major problem in the patient's long illness.

CASE 6. A. R. (J.H.H. 546233), a 37-year-old woman, had for 10 years consumed about ½ pint of whiskey daily. She was admitted to the hospital with hepatomegaly, edema of the legs and ascites. She was confused and disoriented and had paranoid delusions about other patients and the attending physicians and nurses. She was thought to have Laënnec's cirrhosis and a "toxic psychosis due to alcoholism." Blood chemical values were as follows: serum bilirubin, 6 mg. per 100 cc.; cephalin flocculation, +++; thymol turbidity, 3.2 units; alkaline phosphatase, 17.5 Bodansky units; prothrombin time, more than 80 per cent of normal; serum cholesterol, 254 mg. per 100 cc.; fasting blood sugar, 48 mg. per 100 cc. Because of delay in receipt of the last report, hypoglycemia was not recognized, but the patient was encouraged to eat frequently, having consumed little but alcohol prior to admission. Within 48 hours she was rational and has remained so during the 18 months of follow-up observation. All subsequent blood sugar determinations have been normal. Ascites and edema disappeared within 1 month, and the liver-function tests gradually improved. Three weeks after admission the cephalin flocculation was 0, thymol turbidity 2.5 units, alkaline phosphatase 7.2 Bodansky units and bilirubin 1.8 mg. per 100 cc. The liver edge is no longer palpable, and liver-function tests are all within normal limits.

Again, there is no pathological proof, but there is compelling clinical evidence, that this patient had reversible alcoholic and dietary liver damage. The hypoglycemia may have been partially the consequence of poor eating, but was almost certainly a manifestation of liver disease. This case illustrates how the mental reaction resulting from hypoglycemia may be confused with some other psychosis. The opportunity for prompt and efficient therapy with intravenous administration of glucose was missed; it was fortunate that the dietary treatment of alcoholic cirrhosis is also a means of correcting hepatic hypoglycemia.

CASE 7. L. T. (J.H.H. 532035), a 40-year-old woman who was a chronic alcoholic, was proved by biopsy to have cirrhosis of the liver. On 8 occasions during 9 weeks' hospitalization for recurrent jaundice, the fasting blood sugar ranged between 56 and 64 mg. per 100 cc. At no time, however, were there recognizable symptoms of hypoglycemia. The results of liver-function tests were as follows (the paired figures representing the values at the beginning and at the end of hospitalization respectively): serum bilirubin, 14.5 to less than 0.8 mg. per 100 cc.; serum alkaline phosphatase, 13.4 to 8.6 Bodansky units; cephalin flocculation, +++ to ++; thymol turbidity, 29.2 to 22 units; serum albumin, 2.9 to 3.1 gm. per 100 cc.; serum globulin, 4.0 to 3.5 gm. per 100 cc.; and prothrombin time, 30 to 35 per cent of normal. In the 2d month of hospitalization, a glucose tolerance test was performed, with the following results: fasting, 64, ½ hour, 180, 1 hour, 170, 1½ hours, 48, 2 hours, 24, 3 hours, 52, 4 hours, 64, and 5 hours, 68 mg. per 100 cc. During the period when the blood sugar values were 48, 24 and 52 mg. per 100 cc., the patient exhibited marked sweating, confusion and obtundity, but she recovered spontaneously and appeared mentally normal during the 4th and 5th hours of the test.

In this case there were no symptoms or signs of hypoglycemia, apart from those observed during the glucose tolerance test, despite the repeated finding of a slightly low fasting blood sugar. During the glucose tolerance test, however, marked lowering of the blood sugar was accompanied by sweating and obvious cerebral dysfunction.

A period of hypoglycemia following the initial elevation of the blood sugar during a glucose tolerance curve is observed in patients with hepatic disease, and those with so-called functional or reactive hypoglycemia. It seems unlikely that in this patient with diffuse liver disease reactive hypoglycemia was the major cause of the low blood sugar values. Seldom, if ever, is simple reactive hypoglycemia associated with persistent fasting hypoglycemia, nor is the blood sugar often as low as 24 mg. per 100 cc. In all likelihood the delayed hypoglycemia was due to the liver disease. The findings in this case indicate the need for a careful study of liver function in patients suspected of having "functional" hypoglycemia.

Case 8. J. H. B. (J.H.H. 413182), a 58-year-old Negro, underwent a total pancreatectomy and cholecystojejunostomy because of an adenocarcinoma of the pancreas. For 2 months postoperatively the "surgical diabetes" was treated with moderate doses of crystalline and protamine zinc insulin. Because of numerous hypoglycemic episodes considered to be insulin reactions, the insulin was discontinued. He ate poorly and was fed principally by infusions of sugar. A week later the urine was acetone free, and the fasting blood sugar was 156 mg. per 100 cc. On the following day the fasting blood sugar was 25 mg. per 100 cc. and he was promptly roused from coma by the intravenous administration of glucose, of which, during the day, he received a total of 5000 cc. of a 10 per cent solution. In the ensuing 2 days, having received no insulin, he was given 800 cc. of 50 per cent glucose and 1500 cc. of 5 per cent glucose intravenously. Nevertheless, when the infusion was discontinued for 1 night, he lapsed into a coma, from which he never recovered. The blood sugar after the night's "fast" was 12 mg. per 100 cc. Blood chemical values in the final week of illness were as follows: serum bilirubin, 38 mg. per 100 cc.; cephalin flocculation, +++; thymol turbidity, 8.5 units; serum cholesterol, 252 mg. per 100 cc.; serum alkaline phosphatase, 55.6 Bodansky units; prothrombin time, 45 per cent of normal; and serum albumin 3.2 and serum globulin 2.6 gm. per 100 cc. Autopsy disclosed metastatic adenocarcinoma of the pancreas in the liver and lungs, biliary cirrhosis and central atrophy of the liver, chronic cholecystitis and a torn hepatic duct (apparently a surgical accident).

This unfortunate patient had severe, resistant hypoglycemia secondary to widespread liver disease. Insulin had been discontinued nine days before his death, and could not have been responsible for the final blood sugar level of 12 mg. per 100 cc. On the contrary, it seems far more likely that the numerous "insulin reactions" early in the course were at least partially caused by the liver damage. In this case hepatic hypoglycemia appeared despite total pancreatectomy. Similarly, in pancreatectomized dogs, which are ordinarily diabetic, hepatectomy produces fatal hypoglycemia.[1]

Case 9. W. R. (J.H.H. 280018), a 30-year-old Negro, had been followed at this hospital for many years because of sickle-cell anemia. His last admission followed a 36-hour period of dyspnea and intense back pain. Congestive heart failure was manifested by pulmonary and peripheral edema, and the liver edge was palpable 6 cm. below the right costal margin and 13 cm. below the sternum. The hematocrit was 19 per cent; the white-cell count was 38,000 with 8 per cent reticulocytes, and there was approximately 36 per cent immediate sickling of the red cells. The serum bilirubin was 20 mg. per 100 cc., cephalin flocculation +++, thymol turbidity 14.3 units, and alkaline phosphatase 6.6 Bodansky units. Shortly after admission the patient lapsed into coma, had generalized convulsions and died. A blood sugar determination on a sample drawn during the coma, but not reported until after death, was 23 mg. per 100 cc. Autopsy demonstrated atrophy and fibrosis of the spleen, "sickle-cell nephritis," recanalized pulmonary thrombi, cor pulmonale, pulmonary and cerebral edema, nodular cirrhosis of the liver, with hemosiderosis, hemosiderosis of the pancreas and kidney, aspiration pneumonia and an acute gastric ulcer.

This case has many points of interest not germane to the present discussion, but illustrates once again that severe hepatic hypoglycemia may appear when other clinical abnormalities are more prominent and obvious.

Case 10. J. C. E. (J.H.H. 595114), a 19-year-old boy, a chronic alcoholic, was admitted to the hospital with a 3 weeks' history of jaundice, malaise and anorexia. Two of his brothers had died of hepatic necrosis, and another brother appeared to be recovering from severe infectious hepatitis. The patient was obviously very sick, with nausea, vomiting, jaundice, low-grade fever and a liver edge palpated 4 fingerbreadths below the right costal margin. The serum bilirubin on admission was 11.2 mg. per 100 cc. and shortly before death 1 week later, 29 mg. per 100 cc. The cephalin flocculation was +++, thymol turbidity 8.2 units, alkaline phosphatase 5.6 Bodansky units, serum albumin 2.9 and serum globulin 3.0 gm. per 100 cc., prothrombin time less than 20 per cent of normal, nonprotein nitrogen 44 mg. per 100 cc., and fasting blood sugar 68 mg. per 100 cc. Despite intravenous injection of glucose and serum albumin, the patient gradually became weaker and more jaundiced. On the day of death he lapsed into coma. A blood sugar determination was 23 mg. per 100 cc. The patient rallied and became lucid after the intravenous administration of glucose, but then, despite continued glucose infusions, again sank into coma and died several hours later. Autopsy showed severe chronic hepatitis.

In this case hypoglycemia was associated with liver failure so severe that intravenous administration of glucose was of only transient value. The situation is reminiscent of Mann's hepatectomized dogs, in which consciousness preserved with intravenous administration of glucose was followed in a day or so by irreversible coma.[1]

Case 11. M. C. (J.H.H. 594910), a 70-year-old woman, was admitted to the hospital in severe congestive heart failure. Four years before admission mild exertional dyspnea, which gradually became worse, had developed, and for 1 year before admission she had been treated with digitalis and mercurial diuretics because of increasingly severe exertional dyspnea, orthopnea and ankle edema. Despite these therapeutic measures the congestive heart failure became much more severe in the month before admission, and in the 5 days preceding admission mild confusion had slowly turned into stupor and nearly complete loss of reason. The important findings on physical examination were cyanosis of the fingers, toes and lips, distended neck veins, marked edema of the ankles and back, rales at both lung bases, enlargement of the heart, with harsh systolic murmurs suggestive of mitral and aortic disease, a tender liver edge palpated 3 fingerbreadths below the right costal margin and very little responsiveness to any stimuli. The patient did not improve in an oxygen tent or in a sitting position in a "cardiac bed." The hematocrit was 56 per cent and the white-cell count 12,000. The urine was remarkable only for a ++ test for albumin and urobilinogen found in 1:200 dilution. The patient's mental status was ascribed to cerebral anoxia, but because of her age and critical condition various blood chemical values were determined. These were as follows: nonprotein nitrogen, 98 mg. per 100 cc.; blood sugar, 16 mg. per 100 cc.; carbon dioxide combining power, 21.6 milliequiv. per liter; and serum chloride, 100.2 milliequiv. per liter. Almost immediately after 50 cc. of 50 per cent glucose had been rapidly injected intravenously, the patient became much less lethargic and disoriented. Thereafter, the blood sugar was maintained above 100 mg. per 100 cc. by slow infusions of 10 per cent glucose and oral

feeding, but despite all measures to improve her cardiac and renal status, the nonprotein nitrogen rose to 134 mg. per 100 cc., and the heart failure became progressively more severe. Marked mental clouding returned on the 3d hospital day; the patient lapsed into coma and died on the 4th hospital day. Before death the following determinations were made: serum bilirubin, 3 mg. per 100 cc.; serum albumin, 3.1, and serum globulin, 2.3 gm. per 100 cc.; cephalin flocculation, +++; and thymol turbidity, 5.3 units. At autopsy the principal findings were calcific aortic stenosis and mitral stenosis, generalized ar eriosclerosis and passive congestion of all the viscera, including the liver, which showed marked central necrosis. There were a few small areas of infarction in the pituitary gland, but these were not considered significant by the pathologist, who pointed out that such lesions are not uncommonly found at autopsy in patients having no clinical evidence of pituitary dysfunction and that the vast majority of the pituitary tissue in this case appeared quite normal.

There can be little doubt that this patient had severe hepatogenic hypoglycemia. It is of interest that the coma, promptly but temporarily relieved by intravenous injection of glucose, was thought to be a consequence of cerebral anoxia until a "routine" blood sugar determination was reported.

The remaining 9 of the 20 cases of hepatic hypoglycemia (summarized in Tables 1 and 2) are not presented in detail because of their similarity to those described above.

TABLE 1. *Summary of Cases of Hepatic Hypoglycemia.*

CASE NO.	PATIENT	AGE	SEX	LIVER DISEASE	OTHER DIAGNOSES	FASTING BLOOD SUGAR	SYMPTOMS OF HYPOGLYCEMIA
		yr.				*mg./100 cc.*	
1	D. B.	27	F	Serum hepatitis	None	44	Schizophrenia-like psychosis
2	J. P.	65	F	Laënnec's cirrhosis	Alcoholism, chronic pyelonephritis, generalized arteriosclerosis and Kimmelstiel-Wilson's disease	8	Coma
3	B. E.	38	F	Passive congestion	Myxoma of left auricle	23	Coma
4	F. H.	70	M	Biliary cirrhosis; metastatic carcinoma.	Adenocarcinoma of pancreas	6	Coma
5	J. L.	71	M	Passive congestion, fatty infiltration and early cirrhosis	Alcoholism, syphilitic aortitis, myocarditis and myeloid hyperplasia	20	Coma
6	A. R.	37	F	Laënnec's cirrhosis	Alcoholism, syphilitic aortic regurgitation and polyneuritis	48	Schizophrenia-like psychosis
7	L. T.	40	F	Laënnec's cirrhosis	Alcoholism	24	Confusion
8	J. H. B.	58	M	Biliary cirrhosis; metastatic carcinoma.	Adenocarcinoma of pancreas (total pancreatectomy)	12	Coma
9	W. R.	30	M	Cirrhosis	Sickle-cell anemia	23	Coma; convulsions.
10	J. C. E.	19	M	Infectious hepatitis	Alcoholism	23	Coma (cholemic coma supervened)
11	M. C.	70	F	Passive congestion	Mitral and aortic stenosis	16	Coma
12	J. H.	21	M	Passive congestion	Constrictive pericarditis; lobar pneumonia.	22	Torpor
13	I. B.	41	M	Laënnec's cirrhosis	Alcoholism, syphilitic aortic regurgitation and polyneuritis	31	Coma
14	G. G.	45	M	Primary hepatoma	Alcoholism; acute bacterial endocarditis.	44	Disorientation (cholemic coma supervened)
15	M. G.	52	F	Infectious hepatitis	None	56	Faintness and palpitation
16	L. R.	41	M	Infectious hepatitis	None	47	None
17	L. S.	25	F	Fatty infiltration	Infection and gangrene of vulva; tuberculous peritonitis; and enteritis.	20	Coma
18	J. S.	45	F	Hepatitis	None	44	Irrational behavior
19	P. H.	32	M	Fatty infiltration	Partial pancreatectomy; subphrenic abscess.	40	Weakness and faintness
20	H. K.	37	F	Passive congestion	Mitral stenosis; ball-valve thrombus of left auricle.	19	Coma

DISCUSSION

Transient hypoglycemia was an important feature in the illness of the patients described above (Table 1). In some cases the episodes of hypoglycemia critically affected the course, contributing to death. It seems reasonable to conclude that impaired liver function was the common cause of these periods of hypoglycemia, since other factors capable of inducing hypoglycemia were absent, and all patients had significant liver disease.

Spontaneous hypoglycemia may occur in the following conditions: islet-cell tumor of the pancreas; hyperplasia of the islands of Langerhans, without adenoma formation; reactive or functional hypoglycemia; adrenal insufficiency; pituitary insufficiency; hypothyroidism; extreme muscular exertion, such as marathon racing; liver disease; and during periods of starvation.[4, 5] Of the 20 cases reported in this paper, autopsies were performed in 13, and in none was there evidence of hyperplasia or adenoma of the islands of Langerhans, adrenal

TABLE 2. *Types of Liver Disease Associated with Hypoglycemia.*

DISEASE	NO. OF PATIENTS
Viral hepatitis	5
Laënnec's cirrhosis	5
Chronic passive congestion, with heart failure	5
Biliary cirrhosis	2
Fatty infiltration	2
Primary hepatoma	1
Total	20

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damage, thyroid disease or pituitary abnormality, except in Case 11, whose insignificant pituitary damage is explained in detail above. All, however, showed unequivocal diffuse hepatic damage on histologic examination. Moreover, there was clinical or laboratory evidence of liver disease apart from the hypoglycemia in all 20 patients, although in some cases liver impairment had not been considered a significant feature of the illness. On the other hand, in none of these patients were there clinical indications of pituitary, adrenal or thyroid insufficiency, nor could extreme exercise, prolonged starvation or reactive hypoglycemia have played an important part in the development of these hypoglycemic states. It is, of course, possible that the 7 patients who did not come to autopsy had islet-cell tumors or hyperplasia, since these entities cannot be excluded without post-mortem examination. There was nothing in the clinical course of these patients to suggest such a condition, however, and it seems reasonable to assume that the hypoglycemia was due to liver disease because of the known association with hepatic impairment and the complete absence of factors indicating another diagnosis. Cases 1 and 15 never had symptoms of hypoglycemia until typical viral hepatitis developed, and the hypoglycemia was present only in association with activity of the liver disease. Case 4 was explored surgically and proved by biopsy to have an adenocarcinoma of the pancreas and biliary cirrhosis; there was no evidence of an islet-cell tumor. Case 7 was also explored surgically, cirrhosis of the liver and chronic pancreatitis being found. Cases 6, 12 and 13 had isolated episodes of hypoglycemia associated with obvious clinical liver disease, which was due to alcoholic cirrhosis in Cases 6 and 13 and to chronic passive congestion of the liver secondary to constrictive pericarditis in Case 12. All 3 of these patients have been followed for many years since the hypoglycemia was discovered, and with improved liver function no further episodes of hypoglycemia have appeared.

The mechanism of hepatic hypoglycemia is not entirely clear. Disturbances of any of the following three recognized functions of the liver may contribute to the development of hypoglycemia: glycogenesis, glycogenolysis and gluconeogenesis.[3] If the liver is unable to store glycogen, the blood sugar may fall during periods of fasting. Similarly, inability of the liver to break down glycogen, as in Von Gierke's disease,[4] may produce hypoglycemia. Possibly of equal importance is the liver's ability to produce glucose from noncarbohydrate precursors.

It is interesting to note in Table 2 the occurrence of hypoglycemia in liver disease of such varying causes. As might have been anticipated, types of liver injury widely different pathogenetically produced the same functional defect.

In some cases the extent of hepatic damage was clinically obvious, the patients having outspoken signs and symptoms of advanced liver disease. In others, however, there was little clinical evidence of liver disease, or the findings indicated a degree of hepatic impairment considered unimportant. Indeed, there were occasions when the development of spontaneous hypoglycemia first suggested the presence of significant liver damage.

Hypoglycemia may appear as liver damage progresses, or it may occur episodically in patients with a more or less stabilized degree of hepatic insufficiency, during periods of sudden stress. Such a stress may result from an alcoholic debauch, an acute infection or an operative procedure. Why these isolated episodes of hypoglycemia occur is not clear. The patient's general condition may otherwise remain unaltered.

In mild form, hepatic hypoglycemia may produce nervousness, increased sweating and palpitations. In more severe states the patient may behave in a bizarre manner and be considered psychotic, or may have convulsions or enter a state of shock. It has long been recognized that there is no constant relation between the extent of depression of the blood sugar and the severity of consequent hypoglycemic manifestations. Likewise, in the cases described above, the severity of hypoglycemic episodes could not be related to the clinically apparent degree of liver impairment. In some patients who were not considered on clinical grounds to have an important amount of hepatic insufficiency profound evidence of hypoglycemia developed. This enigma was no doubt due in part to the difficulties inherent in assaying by clinical methods the extent of liver damage.

In most of the cases reported above, the real nature of the hypoglycemic episodes was not immediately recognized, thereby emphasizing the difficulty in diagnosis. This is in no small part due to the lack of awareness of many observers that hypoglycemia is not uncommonly caused by liver disease of many sorts. Again, the manifestations of hypoglycemia are nonspecific, and may be confused with other causes of disordered behavior. An important consideration is the fact that a hypoglycemic episode may occur in a complicated setting in which other manifestations of disease, such as cardiac failure, are so prominent that the evidences of hypoglycemia are completely overshadowed or misinterpreted. Finally, as already stressed, hypoglycemia due to hepatic insufficiency may occur at a time when the usual features of extensive liver damage are not clinically apparent, making recognition of the etiologic relation most difficult. Hepatic hypoglycemia will be detected when the observer is aware of its potential occurrence in any circumstance in which liver function is impaired, though perhaps unobtrusively, and at times when other manifestations of the underlying pathologic process are more prominent.

The 5 patients in whom hypoglycemia developed during the course of congestive heart failure deserve particular attention. Hepatic hypoglycemia occurring as a complication of congestive heart failure has not hitherto been emphasized. The important implications of such an occurrence are obvious. Chronic passive congestion of the liver of long standing was the underlying process in all cases. Loss of appetite and inadequate food intake, which are common in pronounced cardiac failure, perhaps contributed to the development of the hypoglycemic episodes. In the light of our experience the frequency with which hepatic congestion and inadequate diets occur during the progress of chronic cardiac failure suggests that hepatic hypoglycemia is a much more common occurrence in chronic cardiac failure than has previously been recognized. It may be especially difficult to detect the existence of hypoglycemia during the course of congestive heart failure. Usually, such patients have had no frank hepatic insufficiency, and the observer's attention is centered upon the more dramatic signs of cardiac abnormality. Any indications of disordered liver function that are present may be obscured by the complexities of the immediate cardiac problem. When palpitations, sweating and unusual behavior resulting from hypoglycemia are observed, they may readily be dismissed as manifestations of heart failure. Cerebral anoxemia may of itself produce altered consciousness or coma. But to assume that these changes are always due to anoxemia alone may preclude simple and effective therapy. Detection and correction of hypoglycemia, therefore, ranks with other essential measures employed in the management of congestive heart failure.

There are few, if any, contraindications to the intravenous administration of small volumes of concentrated glucose, and this simple test will usually effect dramatic and diagnostic improvement if hypoglycemia is the cause of mental clouding or coma. It is wise, however, if possible, to draw blood for a sugar determination before the glucose is injected. If hypoglycemia has been present for a long time, there may be persistent mental damage that will not readily respond to administration of glucose. Sometimes, indeed, prolonged hypoglycemia may produce irreversible cerebral damage.

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THE TREATMENT OF WRINGER-ARM INJURIES*

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BOSTON

THE term, "wringer arm," was first coined in 1938§ to describe an accident occurring in early childhood in which the upper extremity is inadvertently caught between the rollers of a power-driven washing-machine wringer. In addition to 26 cases previously reported, 116 children with this injury have been treated at the Children's Medical Center, Boston, from 1937 through 1951. In recent years there seems to have been a marked decrease in the incidence of this type of accident, probably owing to the perfection of emergency-release devices on automatic wringer machines and to the wider use of machines equipped with a centrifugal spin-drier mechanism. However, as long as power-driven roller wringers are used in households, wringer-arm injuries will continue to occur. Therefore, a summary of the methods of treatment that have proved successful in the handling of these children may be of interest to the physician or surgeon who is called upon to treat such patients.

Often, this injury occurs during the first week's possession of the machine, for it is at this time that the child is most fascinated by the turning rollers, and the mother is least aware of the potential dangers. There are several factors that influence the severity of the injury. Less damage will be incurred if the mother remains calm and simply strikes the safety-release bar. Too often, she follows her natural impulse to apply counter traction to the child, or to reverse the direction of the rollers, thereby subjecting the arm to a second crushing. The injury will be less severe if the child is very young, since the arm is smaller and the tissues are more yielding. The injury will be more severe if the setting of the rollers is tight, or if the arm is imprisoned between the rollers for any appreciable time. Usually, the axilla or the supracondylar region is the most severely affected, for it is in these areas that the rollers churn about for the longest period.

Because the experience is terrifying to both the parent and child, over 80 per cent of patients were

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taken immediately to a physician for treatment. On examination the arm is usually found to be diffusely swollen and ecchymotic in several areas. There may be many small abrasions, but there is seldom a laceration or avulsion of the skin. Because the initial examination is generally made shortly after the accident, the swelling and discoloration are rarely marked. This might lead the attending physician to underestimate the severity of the damage to the underlying structures.

FIGURE 1. *A Wringer Injury Received Two Hours before Admission to the Hospital, Showing the Arm at the Time of the First Change of Dressing, Twelve Hours Later. (Note the Ecchymotic Areas in the Axilla and above the Elbow).*

During the first twenty-four or forty-eight hours after injury, a guarded prognosis should always be given. The temporary ischemia from the crushing is soon followed by regional edema of the damaged tissues. In the more extensive grades of injury, this is followed by an extravasation of blood beneath the fascia or skin. This collection of fluid elevates the skin so that on palpation a soft, floating type of fluctuance is found. When the fatty layer has been torn from its deep and superficial attachments a sensation of crepitus may often be elicited. Progressive tension of these tissues, enhanced by a slow seepage of blood from damaged vessels, may produce an ischemia of the overlying skin, particularly in the antecubital fossa. This can be followed some days later by cutaneous necrosis and sloughing. If increasing tension is not relieved surgically, a Volkmann ischemic contracture may be produced. Even though these wounds are reasonably clean, the injured skin is a good medium for bacterial growth. Every effort should be made to cleanse the area with a mild antiseptic and to minimize infection. Much has been written about the so-called crush syndrome, which theoretically occurs when muscles are severely traumatized; in this series of wringer-arm injuries no renal dysfunction was observed.

In spite of the fact that severe injuries to the bones, nerves or large vessels seldom occur, examination for and treatment of these must be borne in mind. Roentgenograms should be taken of the extremity in every case. Fractures of minor importance were discovered in 4 of 116 patients. There were 2 greenstick fractures of the humerus or clavicle and 2 linear fractures through the base of the first or fifth metacarpal bone.

TYPE AND EXTENT

In this series of 116 wringer injuries, the patients were classified according to the degree of trauma sustained. The first group of 70 patients (61 per cent) comprised those with simple abrasions and contusions. They were all seen within twelve hours of the accident and were admitted to the hospital for forty-eight hours of observation. Each one recovered completely without demonstrable scars or impairment of function (Fig. 1 and 2).

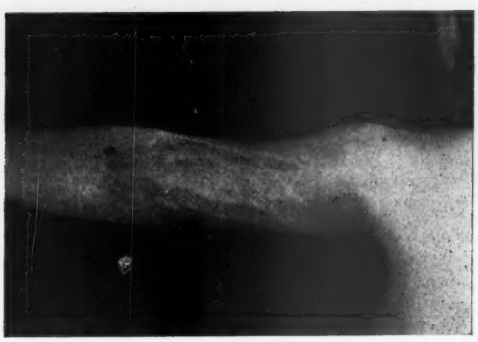

FIGURE 2. *Patient Shown in Figure 1.*
The whole arm was swollen, as shown by the skin marks from the compression bandage. Recovery was complete and without residual defects.

The second group was made up of 23 patients (19.5 per cent), who also were seen within twelve hours of the accident and admitted to the hospital,

but who apparently had received more marked compression injury. In this group tissue effusions developed, requiring incision, drainage and release of entrapped fluid. Twenty-two of the 23 patients recovered completely, the only residuum being the scars from the incision and drainage (Fig. 3 and 4).

FIGURE 3. *Appearance of a Patient Seen Half an Hour after a Wringer Injury, when a Compression Bandage was Applied. The tension and swelling continued to increase; after twenty-four hours this photograph was taken, and incisions were made in the axilla and upper arm, to release the entrapped fluid.*

One patient required grafting to cover a devitalized area of the upper arm.

The third group (19.5 per cent) was made up of 23 patients who had apparently received a severe crushing, but whom we first saw from two days to six months after the injury. A careful review of the case histories revealed that they had received either no treatment or inadequate treatment immediately after the injury. All 23 patients required skin grafting to cover denuded areas, which had resulted from a slough of necrotic tissue (Fig. 5, 6 and 7). It is quite likely that much of the sloughing and also the necessity of grafting could have been prevented if these patients had received early therapy in the form of incision for drainage of the entrapped subcutaneous fluid.

TREATMENT

We are convinced that the vast majority of children with wringer-arm injuries should be hospitalized for a day or two, because at the end of that time the injury may appear to be much more alarming than it did at the time of the initial examination. The preliminary step in treatment is to cleanse the injured areas throughly with gauze sponges soaked first in saline solution and then in Phisoderm. The extremity is placed on a sterile towel, and a limited débridement of any loose skin performed. Great care must be exercised because the demarcation between vital and necrotic tissue may be indistinct at this early stage. Any damaged skin is then covered with *tulle gras* (an autoclaved dressing consisting of wide-meshed paraffined gauze impregnated with vaseline containing 1 per cent compound tincture of benzoin and 1 per cent balsam of Peru). Over this is placed a layer of sterile dry gauze and then either gauze fluffs or cotton, followed by an external wrapping

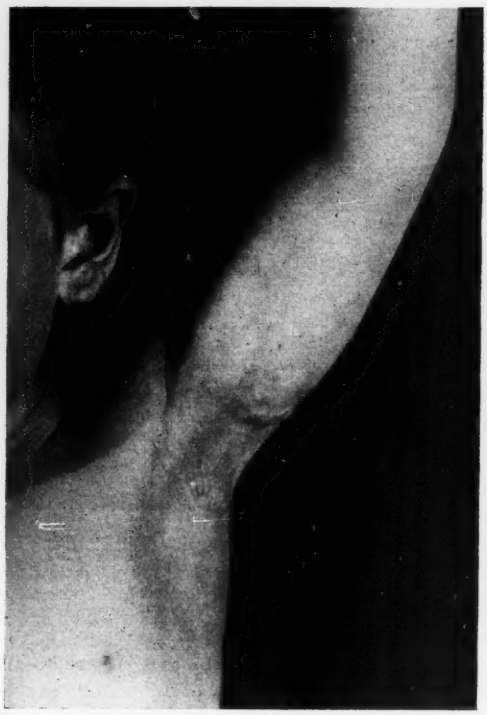

FIGURE 4. *Residual Scars One Year Later (Patient Shown in Figure 3).*

of loosely applied roller bandage. To give compression, the entire dressing is then covered by a

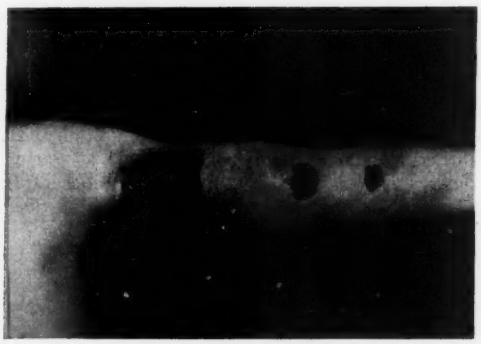

FIGURE 5. *Appearance of a Patient with a Severe Injury Followed by Subcutaneous Effusions That Were Not Drained, Showing Granulations after Preparation for Grafting. The overlying skin and subcutaneous tissue became devitalized and sloughed away.*

snugly applied elastic bandage, started at the fingertips and carried evenly up to the axilla. Inclusion

FIGURE 6. *Injured Areas One Month after Application of Split-Thickness Razor Grafts.*

of the entire extremity in the dressing prevents the development of painful edema of the fingers. During the first forty-eight hours after injury, the patient may require mild sedation; he should be restrained with the arm elevated above the level of the shoulder.

All patients, regardless of whether the injury is fresh or many days old, are placed on a simple antibacterial regimen. Procaine penicillin, 300,000 units per day, and sulfadiazine, 60 mg. per pound of body weight, adequately control most of the contaminating organisms. In cases with secondary infection of sloughed areas, cultures of the organisms and subsequent sensitivity studies aid in selecting the drugs of choice that may be used for continuing the chemotherapy.

One of the most important features of care consists simply in multiple inspections of the wound

FIGURE 7. *Injured Arm Thirteen Years after Grafting.*

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during the first few days to determine the extent or advance of the injury. The first change of dressing is made about twelve hours after admission. If at this time, as we found in 61 per cent of the cases, a good radial pulse is present, the induration and edema are less, and there is no fluctuation, another sterile *tulle-gras* pressure dressing is applied. A second change of dressing is made during the succeeding twelve-hour period. If evidence of more extensive tissue damage is not found, another sterile wrapping is applied. If this same general picture exists on the following day, a third dressing is done, and the patient sent home, to be followed as an ambulatory case. If injury or subcutaneous collection of fluid is advancing, appropriate therapy should be undertaken.

The importance of a short period of hospitalization is well emphasized by the sequence of events that occurred in 23 patients, who required incision and drainage for release of fluid and blood that

had collected beneath the skin. Increasing swelling of the tissues and impending necrosis of the overlying skin became apparent twelve to thirty-six hours after the child had been admitted to the hospital. As soon as these findings had been discovered, incision and drainage were carried out under general anesthesia. The extremity was again thoroughly cleansed and properly draped. An incision was made directly over the area of fluctuance and carried downward through the superficial fascia to the localized collection of fluid. After the evacuation of fluid, blood or clot, the subcutaneous cavity was thoroughly but gently irrigated with physiologic saline solution to remove any residual blood, devitalized tissue or free fat. Then the fascia covering the muscle bundles was inspected. If this was under tension, it was incised to facilitate the return of the deep circulation. The skin incisions were then appropriately sutured, the wound covered with *tulle gras*, and a pressure dressing applied. In cases in which there had been large fluid collections and extensive damage, a soft-rubber drain was left in place for twenty-four hours. When this dressing was changed on the following day, the arm was carefully palpated to milk out any further collections of fluid, and if there were none, the drain was removed. The pressure dressing was reapplied daily until the wounds were healed and edema had disappeared.

In the third group of 23 patients, who had sloughing of skin and who therefore required grafting of skin to close the defect, periodic cleansing accelerated the demarcation between the gangrenous and viable portions of the wound. In such cases, to prepare the granulations for grafting, the arm is given a daily soak in physiologic saline solution for thirty minutes, after which the raw area is covered with *tulle gras*, and a pressure dressing applied. Such treatments are continued until the granulations are clean and cherry pink, indicating sufficient return of circulation to support a free graft. Under general anesthesia, one prepares the raw areas by scraping away all the granulations until a smooth, fibrous-tissue base is reached. This base is cross-hatched thoroughly or even removed completely to prevent a late wrinkling of the graft from deep fibrosis. The denuded area is then covered by a split-thickness razor graft. The graft is covered with *tulle gras*, which in turn is followed by gauze sponges soaked in 1:5000 acriflavine, dry gauze, roller bandage, elastic bandage, splint and stockinette. This dressing is not changed until the seventh or eighth postoperative day, when healing is usually complete. Protective dressings are maintained for another week, and then physiotherapy is started. Conscientiousness on the part of the physiotherapist and patient will result in the normal motion of all joints within six months of the grafting. The cosmetic effect will be satisfactory at this time because proliferation of a new subcutaneous layer beneath the graft compensates for the depression produced by the loss of subcutaneous tissue. When damage has been intensive, deep isolated islands of scar tissue, not only under the graft but elsewhere in the arm, may cause some unevenness of contour. This usually disappears as the child grows.

Summary

To a study of 26 cases of wringer-arm injury previously reported, 116 cases are added. A study of this material emphasizes the importance of hospitalization for at least forty-eight hours after such an accident, regardless of the initial appearance of the injured arm. During this time, periodic examination under sterile precautions permits the attending physician to recognize and release any collections of fluid beneath the skin.

In 70 patients no fluid collected; recovery was rapid and complete. In 23 other patients incisions for evacuation of subcutaneous fluid and blood were necessary to save the overlying skin from necrosis; in only 1 case did such an evacuation fail to save the over-lying skin. In 23 patients who were not seen or hospitalized during the first few days after injury, the failure to evacuate large subcutaneous collections of fluid almost invariably resulted in a slough of the damaged skin and subcutaneous tissue. When necrosis occurred, skin grafting followed by physiotherapy was necessary to restore satisfactory appearance and function.

THE TREATMENT OF ACUTE HEMOPHILIC HEMARTHROSIS*

A Report on the Use of Hyaluronidase

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BOSTON AND PHILADELPHIA

THE extreme disability that follows repeated hemorrhage into various joints is well known to those who care for adolescent and adult patients with hemophilia. The pain and limitation of motion accompanying acute hemarthrosis often lead to a chronic deformity through capsular thickening, contractures, periarticular fibrosis and secondary arthritis. Sooner or later, one or more extremities show one or more partially ankylosed joints, and the patient may become a wheelchair invalid. Typical contractures, as in the knee, may respond slowly to prolonged treatment of wedging casts, stretching, physiotherapy and braces. The social and financial loss, as well as the psychiatric disability to the patient, is tremendous. The end results are poor. The medical literature on the trials of the orthopedist in trying to overcome these fixed and painful deformities is well documented.[1, 2] It is only natural that a means of preventing or at least delaying such an end result is sought. In the past the treatment of a fresh hemorrhage into a joint has consisted of splints, ice bag, sedation and, after all pain has subsided, cautiously administered physiotherapy. The isolation and purification of the enzyme hyaluronidase has allowed increasing use of this drug in many clinical fields. We have been using this agent since 1950 in the treatment of sprains, fresh fractures, hematomas and other orthopedic problems resulting from edema and hemorrhage. These results will be reported at a later date. Britton and Habif[3] have done considerable work in studying its physiologic effect on the spreading of tissue fluids, and have called our attention to the fact that hyaluronidase will hasten the absorption of blood from a joint.

Physiology

Hyaluronidase is produced commercially as the organic extract of bull testes. It acts directly on the ground substance normally present in intercellular substrate. The enzyme causes a depolymerization of the mucopolysaccharide hyaluronic acid, the principal component of the ground substance. With the depolymerization these natural barriers are broken down, and a freer flow of fluid through the intercellular space is obtained. The intercellular fluid when aided by a mechanical pressure, usually external, may thus diffuse through a much greater tissue area than when forced by external pressure alone. With greater dispersion there is a greater area for fluid absorption, and upon this circumstance rests the fundamental mechanism of action.

Hyaluronidase also acts on the hyaluronic acid that forms the bulwark of the synovial fluid. The result is a decreased viscosity. This in turn allows for greater ease in the dispersion through the synovial membrane and soft tissue. Moreover, the enzyme increases the permeability of the synovial membrane as described in the preceding paragraph and demonstrated experimentally by Seifter et al.[4] The end result of this effect of hyaluronidase injected into a joint space is a greatly accelerated dispersion of joint fluid.

Method of Treatment

At the New York Orthopaedic Hospital this drug has been used to hasten the absorption of hemorrhage in fresh hemophilic hemarthrosis since 1950. The number of cases is small, since the diagnosis is not frequent and yet the results are striking enough to warrant a description of the method.

As soon as the diagnosis of an acute hemorrhage has been made, the usual laboratory tests — including the venous clotting time, blood counts and urinalysis — are carried out. Arrangements are made for the prompt infusion of plasma or fresh blood in an attempt to reduce the clotting time to normal and to arrest any concurrent hemorrhage. The joint is then aspirated under strict aseptic technic. No attempt is made to empty the joint cavity completely. Only a few cubic centimeters are removed, for the high viscosity prevents complete aspiration. Then, with the needle still in place to obviate a second puncture, 1000 turbidity-reducing units of hyaluronidase§ mixed with 1 per cent procaine is instilled into the joint. We are careful not to inject a greater volume of fluid than has been aspirated, for this tends to distend the joint for a few minutes and cause considerable pain and spasm. In actual practice, 4 or 5 cc. of injected fluid is usual for the major joints.

Immediately on withdrawal of the needle a dry sterile dressing is held firmly against the puncture site to prevent oozing. An Ace bandage is firmly applied to provide the extra pressure that has been found to be an essential part of the treatment. No attempt is made to move the joint for twenty-four

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§The hyaluronidase used in this study was kindly supplied by Wyeth, Incorporated, Philadelphia.

hours. At the end of that time the bandage is removed, and the joint evaluated for residual distention and pain and for active and passive motion. If the examination reveals significant signs and symptoms, the treatment is repeated. At the end of the second twenty-four-hour period the results are usually satisfactory, and the patient may be allowed to go home, full use being permitted and encouraged. Such freedom of action was not possible under the former conservative management.

Analysis of Cases

Thirteen cases of acute hemophilic hemarthrosis have been treated in the last two years (Table 1). In several cases patients returned in the following months with a fresh hemarthrosis so that the actual number of patients involved was only 6. In all cases the diagnosis was thoroughly established by the usual criteria. When first treated with hyaluronidase all patients already had early or late manifestations of joint changes from previous and repeated hemorrhages.

Table 1. *Analysis of Cases.*

Patient	Age	Case No.	Joint	Duration of Hemorrhage	Arc of Motion		
					Before Treatment	At 24 hr.	At 48 hr.
	yr.						
P. S.	15	1	Left elbow	24 hr.	Flexor-extensor, 5°	15°	25°
		2	Left elbow	12 hr.	Flexor-extensor, 45°	110°	Not recorded
L. D.	4	3	Right shoulder	12 hr.	Abduction, 45°	90°	Not recorded
					Internal and external rotation, 25°	110°	Full
B. S.	22	4 (10/3/50)	Left elbow	3 days	"Markedly limited"	Suprapronation, full Flexor-extensor, 30°	Full 75°
		5 (3/23/51)	Left elbow	20 hr.	Flexor-extensor, 10°	45°	105°
		6 (9/25/51)	Left ankle	Not recorded	Dorsiflexion, 0° Plantar-flexor, 0°	Not recorded	Not recorded
		7 (10/29/51)	Right elbow	12 hr.	Flexor-extensor, 30° Suprapronation, 90°	30° 90°	30° 90°
		8 (11/12/51)	Left ankle	60 hr.	Plantar-flexor, 0° Dorsiflexion, 0°	40°	Full
J. S.	9	9	Right knee	4–5 days	Flexor-extensor, 30°	0°	80°
J. M.	10	10 (9/28/51)	Left elbow	2 wk.	Flexor-extensor, 120° Suprapronation, full	130° Full	130° 130°
		11 (9/28/51)	Right ankle	5 days.	Dorsiflexion, 0° Plantar-flexor, 0°	25°	Full
		12 (4/16/52)	Left elbow	2 days	Flexor-extensor, 10° Suprapronation, 0°	70° 150°	105° 150°
F. M.	9	13 (5/27/52)	Right elbow	1 wk.	Flexor-extensor, 70° Suprapronation, 40°	90° 60°	120° 70°

Discussion

Table 1 demonstrates that the results were successful in 11 cases, as judged by a rapid relief of pain and the equally rapid restoration of a normal range of motion. It is possible to reduce hospitalization substantially — indeed, it would be possible to treat the patient on an outpatient basis — if transfusions or observation for other sites of hemorrhage were not necessary. Some patients have serious bleeding elsewhere at the same time of hemorrhage into a joint. Statistical analysis of the length of hospital stay is thus necessarily invalid.

In the successful cases pain is practically absent or greatly relieved at the end of the first twenty-four-hour period and completely absent forty-eight hours after injection. This relief is associated with a marked improvement in the range of motion, both active and passive. At the end of the forty-eight-hour period the former range of motion is restored. Joint distention is greatly diminished at the end of the two-day period. The relief of pain, the reduction of distention and the return of complete motion allow full and early use of the upper extremity or complete weight bearing on the lower extremity at the end of the forty-eight-hour period. In comparison with previous hemorrhages in the same joint in the same patient, recovery is not only greatly accelerated but also more complete in the enzyme-treated joint. Morale is greatly improved, and this alone is quite an achievement in most patients with hemophilia. We are convinced that hyaluronidase will be a definite aid in the prevention or postponement of contractures through the restoration of early painless motion. With the rapid restoration of normal synovial fluid, the nutritional source

of cartilage is restored, and degeneration is forestalled.

There were 2 failures (Table 1), both of which can be readily explained. Treatment in 1 case was unsuccessful because the first injection was not into the joint. When the joint was reinjected the next day we were able to ensure that the fluid actually entered the cavity. Twenty-four hours later the joint had a full and painless range of motion.

The other failure occurred in a struggling, apprehensive child. After forty-eight hours tension was diminished, and the range of motion had increased. The joint was then reaspirated to obtain fluid for analysis. At the time of reaspiration the child struggled to such an extent that a nosebleed developed. About six hours later it became evident that a fresh hemorrhage in the same joint was also developing. Because of the apprehension and febrile course, it was decided to stop active treatment. Six weeks passed before range of motion was restored. It is essential that children be properly sedated before aspiration of any joint is attempted; neglect of this point was a major contribution to failure in the case mentioned.

There were no reactions to the use of hyaluronidase itself, and no toxic manifestations. It is true that the danger of procaine reaction should be anticipated. Although we have not seen such reactions from the rapid absorption of procaine in a relatively short period, others have, and the use of a barbiturate before injection is advised.

It has been stated by most writers that aspiration of a hemophilic joint is contraindicated. This has not proved to be a problem, for hemorrhage at the site of aspiration did not occur in these cases. Should it develop, pressure over the point of bleeding, if maintained for an adequate length of time, will allow clotting.

The dose of hyaluronidase has not been thoroughly or accurately determined for these cases. It is advisable to give 1000 turbidity-reducing units in 4 cc. of procaine for each joint. This dose was effective in all cases. Larger amounts will not increase the speed of recovery.

TABLE 1. (*Concluded.*)

PATIENT	PAIN			DURATION OF HOSPITAL STAY	FINAL RESULT	COMMENT
	BEFORE TREATMENT	AT 24 HR.	AT 48 HR.			
P. S.	++++	+++	++	3 days	Satisfactory	Patient treated by another service; insufficient data for evaluation, but patient pleased with results of treatment.
	++++	+	Not recorded	36 hr.	Satisfactory	
L. D.	++++	+	0	48 hr.	Fair to satisfactory	First injection missed joint; excellent result followed reinjection.
B. S.	++++	++	+	3 days	Satisfactory	
	++++	+	0	3 days	Satisfactory	
	++++	+	0	5 days	Satisfactory	Insufficiently recorded data, but patient stated he was "95 per cent" better in 48 hr.
	++++	++++	++++	4 days	Satisfactory	Full motion without pain on 4th day; 1st injection contained excessive fluid, necessitating 2d injection 24 hr. later.
	++++	+	0	28 hr.	Satisfactory	
J. S.	++++	++++	++	3 wk.	Fair	Patient responded adequately; after 48 hr. reaspiration performed, with considerable struggling by patient and new hemorrhage; treatment discontinued.
J. M.	++++	0	0	10 days	Satisfactory	Bleeding elsewhere necessitated long hospital stay
	++++	+	0	7 days	Satisfactory	Treatment started 3 days after admission
	++++	0	0	3 days	Satisfactory	
F. M.	++++	0	0	3 days	Satisfactory	

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SUMMARY

A method allowing the rapid restoration of a free range of motion without pain in the acute hemarthrosis of hemophilia is described. Hyaluronidase, through the action on the ground substance of the synovial fluid and synovial membrane, allows the reabsorption of the joint hemorrhage, with resulting freedom from pain and increased motion. With the rapid return of normal synovial fluid, the nutritional source of the articular cartilage is assured, and de-

generation forestalled. The advantage of this technic over previous methods is discussed.

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MEDICAL PROGRESS

EXPERIMENTAL PRODUCTION OF CONGENITAL ANOMALIES*

Timing and Degree of Anoxia as Factors Causing Fetal Deaths and Congenital Anomalies in the Mouse

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THE purpose of this communication is to sketch the status of acquired congenital anomalies of the mouse against a background of experimental embryology; to report progress in the induction of such anomalies by oxygen lack of different degrees maintained for a five-hour period during pregnancy; and to analyze the part played by fetal age (stage of development) as well as anoxic stress.

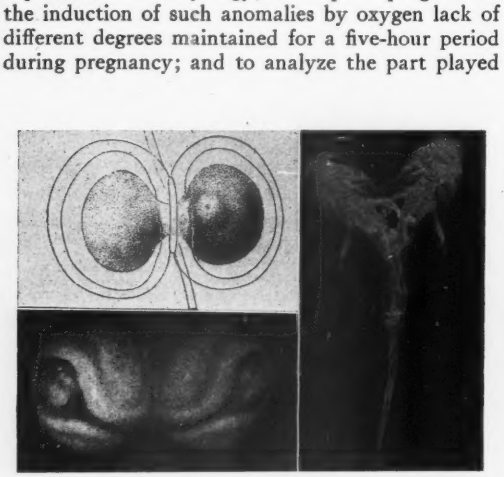

FIGURE 1. *Conjoined Twin Induced in the Egg of the Newt by Ligation of Blastomeres (after Spemann[6]).*

With such excellent monographs as those of Needham,[1] Brachet[2] and Weiss[3] available, no attempt is made to review the massive body of embryologic knowledge; the literature on the biology[4] and genetics[5] of the mouse alone is voluminous. To indicate highlights is not to review a field. A point of departure of this presentation lies about the turn of the century in the contributions of Chabry, Roux, Dreisch and Hertwig in marine biology and those of Panum, Reichart and Dareste, nineteenth-century students of abnormal development of the chick embryo. The demonstration by Roux that one primordial cell of the morula may differentiate independently from its neighboring cells was followed by Spemann's induction of a conjoined twin monster (Fig. 1) by ligation of differentiating blastomeres of the newt.[6]

The interest aroused by these and other investigations was sustained, and around 1910, Stockard[7] succeeded in suppressing normal development of the eyes of the fish, *Fundulus heteroclitus*, by chemical injury of the embryo between the thirteenth and fifteenth hours of embryonic life, the result being cyclopia (Fig. 2). Important findings were that many different agents — chloroform, alcohol, ether and acetone — could induce the same malformation, but only when acting while the optic anlage was in the earliest stages of differentiation. It is noteworthy, too, that all the agents employed were

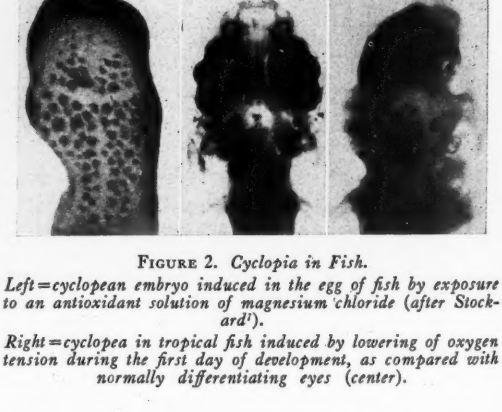

FIGURE 2. *Cyclopia in Fish.*

Left = cyclopean embryo induced in the egg of fish by exposure to an antioxidant solution of magnesium chloride (after Stockard[7]).

Right = cyclopea in tropical fish induced by lowering of oxygen tension during the first day of development, as compared with normally differentiating eyes (center).

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antioxidants, and this fact is part of the rationale that prompted the planning of the present experiments designed to deprive the mouse fetus of oxygen by the device of reduced atmospheric pressure. The work of Stockard and other students of marine biology demonstrated another principle governing malformations of the embryo: that a particular agent gives rise to many different structural changes depending on the time in embryonic life during which it acts.

Subsequently, these principles governing malformations of marine animals were found to apply to congenital malformations experimentally produced in mammals. After Hale's[8] observation that vitamin A deficiency during pregnancy may cause anophthalmos and cleft palate in pigs, Warkany et al.[9, 10] broadened the base of investigation by showing that rachitogenic and riboflavin-deficient diets of pregnant rats registered an impact on the unborn young. Other investigators, stimulated by Gregg's[11] recognition of the influence of maternal rubella in human defects, revealed the teratogenic potentialities of toxoplasmosis[12]; further experimental studies on rodents implicated folic acid and pantothenic acid[13] deficiencies and antimetabolites.[14] Congenital deformities of rats or mice have been brought about by injection into the gravid animal of the colloidal dye, trypan blue,[15] and by anoxia[16] and certain anesthetics such as urethane,[17] as well as by fetal-maternal stress produced through x-ray injury,[18, 19] cortisone injections[20] or artificially produced shock.[21] The present status of experimental teratology was recently summarized by Ingalls[22] as follows:

> From the welter of investigations has come an ever-growing list of teratogenic agents. As the list grows steadily larger one is reminded of Conklin's enumeration[23] of stimuli capable of causing artificial parthenogenesis — mechanical, chemical, thermal, electrical, and radiant. They include light, density of medium, gravity and centrifugal force; oxygen, carbonic acid, water food, secretions of ductless glands; salts, acids, alkalis, alcohol, ether and tobacco. The number of teratogenic agents is not yet as large as the number of parthenogenetic substances — or carcinogens of which some 400 hydrocarbons alone have been identified. As the number rises, however, the question of specificity seems to become less important than dosage and timing of the agent used. The very diversity of teratogenic stresses and agents suggests that any substance that can kill, can induce abnormal growth when acting in critical dosage at an appropriate moment of development. If this is so, then one of the important problems that confronts laboratory investigators is to study some agents quantitatively as well as qualitatively; measuring time when administered as well as dosage of agent; and measuring effects not only in terms of embryonic malformations but also in terms of embryonic mortality.

This has been the objective of the laboratory study presented here. It represents a systematic extension of previous work demonstrating that anoxia of the pregnant mouse may cause intrauterine death or congenital deformity of the fetus, and that the effect varies with the degree of anoxia and stage of fetal development.[16] The preliminary report described the results of a single exposure to simulated high altitude a week or more after fertilization of the ovum. The evidence indicated that anencephaly ("cranioschisis" may be the more accurate term for the defect induced) is but one manifestation of disturbed fetal development secondary to anoxia around the eight or ninth day, cleft palate after anoxia on about the fourteenth or fifteenth day and open eye after anoxic stress toward the end — the fifteenth to the seventeenth day of gestation. In the two years that have elapsed since the first report was published, experiments have been extended with larger numbers of animals to clarify further the influence of timing and degree of anoxia.

Materials and Methods

Strain of Mice and Breeding Habits

The strain of unpedigreed white mice used in this study has been maintained in the laboratory of the Harvard School of Public Health for over five years on an unsupplemented diet of Purina dog-chow checkers, with food and water available to the animals at all times. During this time no outside mice have been introduced into the colony.

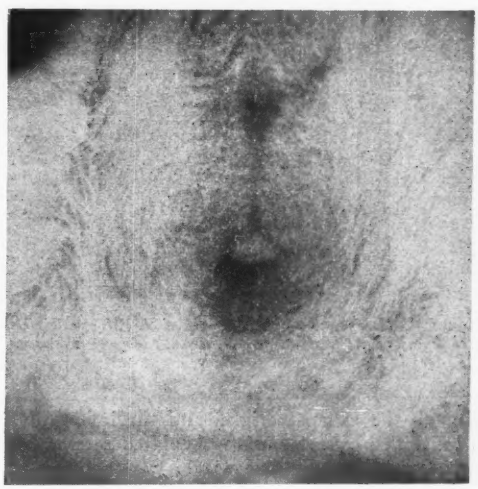

Figure 3. *Copulation Plug in the Vagina of the Mouse.*

Breeding females regularly produce an average of more than 8 offspring per litter, except during the hottest part of the summer, when reproduction all but ceases. Breeding mice are less than a year old, and about 80 per cent of the females are virgin, the remainder having had one previous litter. In mating, care is taken to exclude pairing of parent with offspring or brother with sister. Time of mating is estimated by examination of the females each morning for a copulation plug (Fig. 3) in the vagina.

Discovery of a plug is taken as provisional evidence that gestation began during the preceding night.[24] The error of several hours in timing is consistent in the same direction, however, and is corrected to a reasonable extent by the addition of half a day to gestational age as determined by the presence of the plug. Thus a full day should be added to all previous published ages.[16] Cranioschisis, for example, is now interpreted as closer to a ninth-day than an eighth-day manifestation of central-nervous-system injury.

Method of Producing Maternal Anoxia during Pregnancy

Pregnant mice are placed in a low-pressure chamber measuring 30 cm. long, 12.7 cm. wide and 15.2 cm. deep, constructed of sheets of plexiglas 1.3 cm. thick. Inlet and exhaust orifices at opposite ends of the chamber are near its floor, with the inlet opening into a reservoir holding 300 cc. of water through which entering air is bubbled to maintain a relatively constant humidity of 80 to 90 per cent. A vacuum pump removes air from the chamber

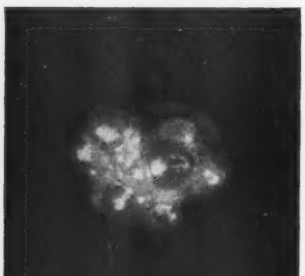

FIGURE 4. *Ovary and Corpora Lutea of the Mouse Dissected Free from the Adnexa on the Nineteenth Day of Pregnancy.*

through the exhaust orifice, and the inflow of air is controlled by a manually regulated needle valve to maintain the pressure within the chamber at a desired level. A mercury manometer is attached to the circuit. The lowest rate of air flow through the chamber exceeds 2.5 liters per minute even at a pressure equivalent to 140 mm. of mercury(about 40,000 feet) — a more than ample volume to prevent oxygen tensions from falling significantly below selected levels even when as many as 6 animals are introduced into the chamber together.[25]

Mice within the chamber receive no food or water, and are free to move about on a wire-mesh screen. Activity diminishes markedly as altitudes approximating 17,000 feet are reached, and all but ceases thereafter. Body temperature drops from an average of 99 to 90°F. after five hours' exposure at 25,000 feet, whereas chamber temperatures average 12°F. lower than room temperatures of 72 to 77°F.

Elevated altitudes are reached gradually to prevent adverse effects (air embolism) upon the animals, about fifteen minutes being taken to reach simulated levels of 25,000 feet (pressure equivalent to 280 mm. of mercury) and 27,000 feet (pressure equivalent to 260 mm. of mercury) used in these experiments. At the end of five hours the procedure is reversed, and the treated animals are gradually returned to sea level (pressure equivalent to 760 mm. of mercury). Beginning on the second day of pregnancy mice have been introduced into the chamber until a total of 10 has been reached for each of the next seventeen days of gestation (second through the eighteenth, inclusive) at each altitude, the grand total being 340 animals. Every third mouse showing a copulation plug is set aside as a control, not being exposed to anoxia but otherwise maintained under the same laboratory conditions as the test animals.

Examination of Pregnant Mice and Fetuses

To prevent the mother from eating dead or deformed embryos, pregnant mice are delivered of their fetuses by a laparotomy after eighteen days (that is, on the nineteenth day) of gestation, a day or two before the litter is due to be born. If such losses are not guarded against, post-partum surveys to determine the incidence of dead and defective fetuses are subject to substantial error. Maternal ovaries are dissected free and examined under the dissecting microscope to count the number of corpora lutea (Fig. 4) for comparison with the number of embryos found.

Each fetus is examined macroscopically and classified as alive or dead (an easy decision) and as normal or anomalous, depending upon the condition of the skin and the organs of the head and the general appearance of the trunk, abdomen and extremities. Fetuses are preserved in 70 per cent alcohol in specimen bottles appropriately numbered for identification. When the fetal tissues are hardened so that dissection may be easily carried out, crown-rump measurements are made, and autopsy is performed to reveal previously undetected malformations.

Under direct vision, incision with a pair of fine scissors is made from the genitalia along the midline of the abdomen and sternum to the region of the clavicle. A lateral incision is also made through the abdominal wall at the level of the umbilicus. The head is severed from the neck at its base with a scalpel; the rib cage is retracted outward with forceps, and the viscera peeled out from above downward. Care must be taken to dissect behind the visceral peritoneum to remove the thoracic and abdominal organs intact.

The viscera are placed, with the posterior surface uppermost, under the dissecting microscope; the

esophagus is divided as it enters the stomach, and the proximal portion lifted free from the trachea for examination for tracheoesophageal fistula, a deformity that has not been found to date. The genitourinary tract is inspected for gross malformations.

The specimen is then turned over, and the lungs, after examination, are pulled away so that the heart and great vessels may be visualized. The relations of the aorta and pulmonary artery are examined. The apex of the heart is held, and the myocardium cut with scissors in such a manner that the ventricles and the interventricular septum are exposed. Finally, the gastrointestinal tract and remaining viscera are inspected for evident defects.

The eviscerated body is cleared and stained to reveal the bony skeleton by means of a conventional method[26] modified as follows: specimens stored in 70 per cent alcohol are placed in 1 per cent aqueous potassium hydroxide solution for forty-eight hours; after the first twenty-four hours, when the bones are readily visible through the translucent tissues, one drop of a 0.5 per cent aqueous solution of Alizarin Red S is added for each 10 cc. of potassium hydroxide; and washing in tap water is done. The process produces a cleared and stained specimen suitable for immediate examination or adaptable to permanent mounting in plastic.[27]

The copulation plug is a practical but imperfect (about 80 per cent accurate) index of pregnancy. Copulation plugs were observed in 138 control females, and 170 females in each of the two test groups. Of the 138 controls maintained at sea level, 24 (17.4 per cent) showed neither living fetuses nor residual evidence of conception. Whether this barrenness represented a failure of fertilization or early embryonic death is not known, but the finding is in fair agreement with the 80 to 90 per cent rate of pregnancy observed by Parkes[28] and Mirskaia and Crew.[29] The 170 females subjected to a reduced pressure of 25,000 feet for five hours during a selected stage of pregnancy had 32 (18.8 per cent) barren uteri, the finding approximating that observed in control mice. In the group of 170 females subjected to an altitude equivalent of 27,000 feet, there were 46 (28.1 per cent) barren uteri. This 10 per cent greater incidence of barren uteri for 27,000 feet is of borderline statistical significance. However, the excess was nearly 30 per cent when exposure at 27,000 feet happened in the first week and over 100 per cent when the maternal stress occurred between the eighth and thirteenth days of gestation (Table 1). These excesses are based on a comparison of the observed number of barren uteri with the number that would be expected had the test group behaved like the control group. It is reasonably clear that when death of the litter occurs in the first half of pregnancy in many animals implantation sites have completely resorbed by the time laparotomy is performed.

Table 1. *Barren Uteri and Altitude by Three Stages of Pregnancy.*

Altitude	Stage of Pregnancy: 1.5–6.5 days		7.5–12.5 days		12.5–17.5 days	
ft.	*Barren uteri observed*	*Barren uteri expected*	*Barren uteri observed*	*Barren uteri expected*	*Barren uteri observed*	*Barren uteri expected*
25,000	12	10.4	13	10.4	7	8.7
27,000	15	10.4	25	10.4	5	8.7

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Corpora Lutea Counts in Relation to Embryos

Counts of corpora lutea at laparotomy on the nineteenth day of gestation were undertaken because they might furnish additional criteria by which to measure embryonic loss. Pregnant mice in the control group had an average of 9.7 corpora lutea per litter and 8.8 embryos, a difference of 0.9, whereas the test mice had more than twice this disparity between corpora lutea and embryos after anoxia in the first week of embryonic life — roughly the preimplantation period (Table 2). This fact and the systematic decrease of disparities in the test periods seven and a half to twelve and a half days and thirteen and a half to seventeen and a half days at both altitudes complement the data of Table 1 and support the inference that single embryos or whole litters may vanish without trace after intrauterine stress early in pregnancy. Presumably, the implantation period is a particularly critical moment in this respect.

Table 2. *Difference in Number of Corpora Lutea and Embryos, by Time of Exposure and Altitude.*

Altitude	Time of Exposure	Average No. of Corpora Lutea per Mouse	Average No. of Embryos per Litter	Difference*
ft.	*days*			
25,000	1.5–6.5	9.8	7.8	2.0
	7.5–12.5	9.7	8.4	1.3
	13.5–17.5	10.2	9.6	0.6
27,000	1.5–6.5	10.7	8.8	1.9
	7.5–12.5	10.0	8.9	1.1
	13.5–7.5	9.7	9.2	0.5
Sea level	(Controls — no exposure)	9.7	8.8	0.9

*Corpora lutea less embryos.

Embryonic Death and Exposure to High Altitude for Five Hours

Of 899 embryos among control animals 111 (12.4 per cent) were dead and in various stages of re-

sorption at laparotomy on the nineteenth day of gestation. Of the 979 embryos subjected to temporary anoxia at 25,000 feet 163 (16.6 per cent) were dead. This is a significantly higher embryonic mortality than was observed among control mice maintained at sea level. In addition to the misshapen dead, 53 living embryos had congenital defects, making the combined morbidity and mortality rate 21.1 per cent.

After exposures at 27,000 feet for five hours, the embryonic mortality was the highest of the three groups of animals: 164 (19.4 per cent) of 847 embryos were dead or resorbing. In addition, 74 living embryos had congenital defects, making the combined morbidity and mortality rate 27.6 per cent.

Death rates arranged according to stage of gestation when females were introduced into the chamber are shown in Table 3. The highest rate of detectable embryonic death was found in the group maintained at 27,000 feet during the second week of gestation (Fig. 5).

TABLE 3. *Fetal Mortality by Altitude and Time of Exposure.*

ALTITUDE	STAGE OF PREGNANCY						TOTAL EXAMINED	PERCENTAGE DEAD
	1.5–6.5 DAYS		7.5–12.5 DAYS		13.5–17.5 DAYS			
	Fetuses examined	*Percentage dead*	*Fetuses examined*	*Percentage dead*	*Fetuses examined*	*Percentage dead*		
Sea level	—	—	—	—	—	—	899	12.4
25,000 ft.	379	12.9	284	15.8	316	21.8	979	16.6
27,000 ft.	221	11.8	232	28.0	394	18.5	847	19.4

FIGURE 5. *Uterine Contents of a Mouse Subjected to Simulated Altitude of 27,000 Feet for Five Hours after Twelve Days — That Is, on the Thirteenth Day — of Gestation. At all but one of nine implantation sites the fetus is dead.*

Intrauterine Distribution of Embryos

The distribution of embryos in verified pregnancies according to location in left or right horn of the uterus was analyzed. No finding emerged to indicate that one side provides a more favorable location for implantation and maintenance of the ovum, even under stress, than the other.

Sex ratios of the embryos were not remarkable: 97.8 males per 100 females among control litters; and 98.6 males to 100 females for both groups of test mice. As yet, no attempt has been made to study the relation of sex to intrauterine deaths and congenital anomalies.

CONGENITAL ANOMALIES

Timing

For the purpose of analysis, congenital anomalies are restricted to a limited number of gross malformations of embryos judged to be alive at laparotomy and arranged in order of onset in Table 4: septal defects (Fig. 6), anencephaly (cranioschisis), irregularities and fusions of ribs and vertebrae (Fig. 7) cryptorchidism (Fig. 8) cleft palate (occasionally associated with micrognathia) and open eye. The number of fetuses with such defects totaled 127, the findings for animals subjected to negative pressures at 25,000 and 27,000 feet of altitude being combined to emphasize timing rather than degree of injury. Fetuses included in the whole analysis numbered 2762, of which all but 37 were delivered by laparotomy; 2337 were processed for skeletal examination. Some of the anomalies — defects of interventricular septum and cryptorchidism — encountered among the test fetuses were observed at low rates (0.1 to 0.8 per cent) among the controls. Cleft palate, anencephaly and hemivertebra, however, were not observed at all in the control group. The frequency with which these 3 defects, as shown in Table 4, were manifest in test animals and their

timing leaves no doubt that they were caused by exposure of the mother to reduced atmospheric pressure.

Many congenital anomalies other than those listed have occurred; hydrocephalus and retinal defects, for example, have been observed in association with open eye.[30] However, a complete macroscopic and microscopic autopsy on every living embryo was not undertaken. Thus, defects of the interventricular septum, anencephaly and cryptorchidism are the sole indexes of cardiac, cerebral and genitourinary anomalies.

TABLE 4. *Congenital Malformations and Timing of Progeny of 340 Copulated Females after Five Hours of Anoxia at 25,000 or 27,000 Feet.*

OBSERVED MALFORMATION	DAY OF PREGNANCY WHEN ANOXIA OCCURRED																	TOTAL
	1.5	2.5	3.5	4.5	5.5	6.5	7.5	8.5	9.5	10.5	11.5	12.5	13.5	14.5	15.5	16.5	17.5	
Defect of interventricular septum	1	0	0	0	3	1	0	0	0	1	0	0	0	0	0	1	0	7
Anencephaly (cranioschisis)	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	3
Hemivertebra	0	0	2*	0	1	0	0	14	37	2	0	0	7	0	2	0	0	65
Fused ribs	0	0	0	0	0	0	0	9	7	0	0	0	0	0	0	0	0	16
Cryptorchidism	0	0	0	0	0	0	0	0	0	0	3	2	0	2	0	7	1	15
Cleft palate	0	1	0	0	1	0	0	0	0	0	2	0	0	9†	0	0	0	13
Open eye	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1	3	2	8
Totals	1	1	2	0	6	1	0	26	44	3	5	2	7	12	3	11	3	127

*Spina bifida.
†2 of these animals had associated micrognathia.

Defects of Interventricular Septum

This deformity was observed in 4 (1.9 per cent) of 210 fetuses from mice subjected to anoxia during the implantation period (Table 4). Otherwise, it was found in 3 (0.2 per cent) of 1465 young from other test animals, and in 1 (0.2 per cent) of 662 control embryos. All defects were large and easily identifiable. More biologically than mathematically significant is the fact that the 4 cases were clustered during the interval of two or three days when the heart is known to be developing its basic contours and compartments.

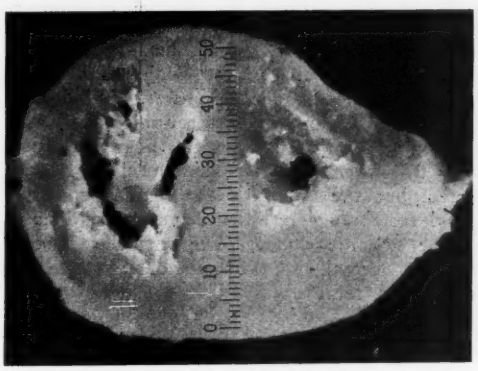

FIGURE 6. *Defect of the Interventricular Septum in the Fetus of a Mouse Exposed at 27,000 Feet on the Eleventh Day of Gestation.*
It is not clear whether the defect stands in chance or causal relation to anoxic stress.

Anencephaly (Cranioschisis)

After maternal anoxia on the ninth day of pregnancy at an altitude of 25,000 feet, 3 of 8 litters each contained 1 anencephalic fetus — 5.7 per cent of the 53 living mice in the 8 litters. These were the only fetuses so affected in a total of 2762 examined for gross defects, including 880 controls not deprived of oxygen. The cerebrum was completely exposed, with congenital absence of the calvarium. Histologic section[16] revealed the membranes and ventricles to have ruptured as a part of the maldevelopment. Cerebral structures and choroid plexus were present but greatly distorted. The question arises whether the anomaly should be called anencephaly or cranioschisis. The difference

FIGURE 7. *Fusions of Ribs and "Hemivertebra" Resulting from Anoxic Stress at 25,000 Feet on the Ninth Day of Intrauterine Life.*

appears to be one of degree rather than kind. It is reasonable to believe that the defect observed is biologically of the same order as the relatively greater anencephaly induced by Russell[18] and Hicks[19] as the result of radiation injury around the ninth day of gestation. It is interesting that the 3 cases observed in these experiments were associated with hydramnios, since the condition is so often associated with the human malformation. Hydramnios, like hydrocephalus, was not measured in this study; it was noted occasionally, however, in association with prenatal deaths — with the dead fetus floating in the excess fluid.

FIGURE 8. *Normal (Top) and Cryptorchid (Bottom) Development of Testis in the Mouse.*
A=*kidney*; B=*descended testicle*; C=*undescended testicle.*

Hemivertebra and Associated Defects of the Spine

Fifty-one (33.3 per cent) of 153 living fetuses had vertebral defects after high-altitude anoxia of the mother on the ninth and tenth days of gestation (Tables 4 and 5). By comparison, comparable defects were not observed among controls and only 12 (0.8 per cent) times among the 1522 remaining test fetuses. The 9th and 10th days of gestation are demonstrated to be a critical period for malformations of the ribs and vertebral column.

Hemivertebra, like anencephaly and many other names for congenital defects, is a loose term for a variable syndrome; it usually consists of vertebral fusions involving two or more articular surfaces or partial fusion of vertebral bodies, pedicles and lamina, affecting one or both sides of the fetus. Associated defects were frequent: fusion of the ribs, for example, in 25 fetuses, and absence of half the vertebral arch, lamina or articular process at a level other than the primary site.

TABLE 5. *Hemivertebra and Fused Ribs by Altitude and Day of Exposure.*

ALTITUDE	DAY OF PREGNANCY	NO. OF EMBRYOS EXAMINED	
		TOTAL	DEFECTIVE
ft.			
25,000	8.5	31	4 (12.9%)
27,000	8.5	54	19 (35.2%)
25,000	9.5	40	24 (60.0%)
27,000	9.5	28	20 (71.4%)

Associated defects of the spine included extravertebral bodies, fragmented bodies and irregular development of bony structures. Spina bifida was found in 2 additional fetuses subjected to anoxia on the fourth day of intrauterine life at an altitude of 27,000 feet. No external abnormality was detected, but the bodies of the lumbar and upper sacral vertebras were absent, and the laminae and pedicle underdeveloped. The articular processes appeared normal, and no other anomalies were found in these 2 fetuses.

Fused Ribs

Sixteen (10.5 per cent) of 153 fetuses showed fused ribs as the only defect, all offspring of mothers deprived of oxygen on the 9th or 10th day of gestation and more at 27,000 feet than at 25,000. The defects ranged from double heads (usually associated with fused vertebras) to bifid bodies of ribs, or fusions at the tip or for varying distances along the body from the angle ventrally. A similar defect was found in only 1 fetus out of 662 examined in the control population.

Cryptorchidism

The undescended testis is distinguished from the normal by the fact that it is attached to the lower

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pole of the kidney with tough, fibrous mesenchyme, rather than being in a normal pelvic location adjacent to the bladder. This defect was present in 15 (0.9 per cent) of 1675 fetuses from the experimental groups, and 5 of 662 (0.8 per cent) fetuses from control mothers. Ten of the 15 cases in test animals were associated with anoxia between the fourteenth and seventeenth days of gestation. The left testis was mislocated nearly twice as often as the right, and about 20 per cent of the fetuses had the defect bilaterally. The occurrence of cryptorchidism may have been influenced by anoxic stress although the numbers involved were too small to establish the point.

Cleft Palate

In the strain of white mice used, only gravid females subjected to reduced atmospheric pressures produced offspring with cleft palate. Thirteen of 1882 fetuses had the defect, the fifteenth day being the critical stage of pregnancy, and the more effective altitude being 27,000 feet. Of 67 fetuses from mothers tested on this day and at this altitude, 9 (13.4 per cent) had the cleft palate, as compared to 4 (0.2 per cent) of 1753 fetuses from mothers introduced into the chamber on other days of gestation (Table 4).

The cleft begins, anteriorly, with midline separation of the posterior portion of the premaxillary palatine process. The palatine processes of the maxilla are vestigial — so much so as to leave a clear space (the cleft) through which the whole of the vomer can be seen. The palatine bones themselves appear as though cut in two, with their medial portions completely absent. The alisphenoids and their inner pterygoid processes are intact. In association with cleft palate after exposure to reduced atmospheric pressure on the fifteenth day of intrauterine life, 2 fetuses in 2 litters had micrognathia.

Open Eye

In the mouse the eyelids normally complete differentiation and fuse around the sixteenth to the seventeenth day of intrauterine life[31] so that normally the eyes are covered by closed lids at birth. When the lids fail to fuse at the proper time, the aperture permits direct inspection of the cornea and globe at birth — so-called open eye. The defect was seen 7 times in as many litters of mice subjected to anoxia during the last quarter of gestation (Table 4), once among progeny of mothers experiencing stress in the first quarters of gestation and in 2 fetuses of the control group. The findings have been presented elsewhere,[30] together with a discussion of similarities of the condition to retrolental fibroplasia.

Discussion

At the beginning of this article Spemann's work was selected as a point of departure for a consideration of accumulated knowledge of experimentally produced anomalies. However, a full appreciation of the nature and importance to mankind of the broad biologic problem antedated Spemann's publications by almost a century. The basic challenge was clearly formulated in Geoffrey Saint-Hilaire's three-volume work *Des Anomalies*, published in Paris in 1836:

> If. . .anomalous beings are created. . .according to natural laws; if their deviations are the effects of disturbances and adverse influences happening during the course of development; if their causes are only accidental — and of this there can be no longer any doubt — another subject for research presents itself, a subject important, immense and capital: the determination of causes.

Although Saint-Hilaire foresaw equally clearly the necessity for experimentation to confirm and clarify his magnificent hypothesis — and indeed engaged in unsystematic study — of the effects of traumatizing and shellacking fertilized hen's eggs — it remained for Camille Dareste (1877) to indicate the direction and necessity for the experimental approach:

> Let us not forget that hypothesis, however ingenious, however reasonable it may be is not science. . .Where then shall we find the elements of teratology? Since direct observation cannot procure them, it is necessary to seek them by experiment.

Dareste instituted a fruitful series of researches on environmental causes of anencephaly, cyclopia, skeletal deformities and cardiac defects in chicks by subjecting embryonating eggs to low temperatures. Unfortunately, the experiments were not carried out in systematic fashion, nor did he present all the facts and measurements necessary for confirmation, continuation and extension of his work.

A more important reason why the work and ideas of these two pioneer thinkers were not carried steadily forward in the last quarter of the nineteenth century was the emergence of Mendel's work, which seemed to show that congenital anomalies were wholly a matter of genetics — and hence of more theoretical than practical interest to practitioners of medicine.

Nor did the investigations of Spemann and others working from 1900 to 1925 go very far toward bringing together the Neo-Lamarckian and Mendelian dichotomy of environment as opposed to heredity. An obvious explanation is that in work on ascidian (sea squirt), sea urchin and fish eggs genetic factors were seldom if ever quantitated, and in the work on higher animals, including man, the influence of events preceding birth was seldom known or taken into account. The work of Landauer and his associates in recent years has been in the direction of measuring both genetic and environmental factors influencing the hatching of eggs, but for mammals it took the clinical discovery of Gregg to act as a persuasive catalyst and forcibly demonstrate the importance of relatively minor and short events. This has rekindled the blaze of controversy

and investigation started in the last half of the nineteenth century.

The conceptual as well as the factual background that has been outlined is pertinent because the method described provides opportunity for measuring the multiple factors that contribute to defective growth during the prenatal period: the causative agent (anoxia), other environmental factors, (such as temperature), the changing (developing) fetus and the genetic constitution of the strain of mouse used. Unpublished work undertaken with Avis and Temin indicates that the number and kind of defects (umbilical hernia, for example) are related to the genetic character of the strain of mouse being studied in addition to the environmental events of pregnancy.

In the experiments reported here the various environmental factors influencing pregnancy were stabilized as far as possible except for atmospheric pressure. Pressure, used as an indirect measure of anoxia, was held at two levels equivalent to 25,000 and 27,000 feet of altitude, and time (development) was measured in twenty-four hour periods of gestation. Under the circumstances of the experiment, results previously reported were confirmed and extended. Anencephaly (cranioschisis) and multiple skeletal deformities followed exposure to a rarefied atmosphere on about the ninth day; cleft palate on around the fifteenth day; and cryptorchidism in the latter half, and open eye toward the end of gestation. In general, induced defects were more numerous and severe at the higher altitude. Exceptions occurred, however, presumably when the lesser stress was experienced at a more critical moment of differentiation. Both timing and degree of anoxic stress are shown to be determining causes of congenital malformations. The causative agent (anoxia) gives rise to many different manifestations, depending not only on when it acts (the ninth as opposed to the fifteenth day of gestation, for example) but on where it acts — the head, as opposed to the spine or the ribs. Anencephaly, hemivertebra and fused ribs, different as they are anatomically, are biologically the same disease in this experiment.

It is reasonable to believe that the mode of action of the low-pressure insult is primarily anoxia of both mother and progeny brought about by lowered arterial oxygen saturation and tension, resulting in low tissue oxygen in mother and fetus and direct local stress of those rapidly differentiating tissues that are known to have a growing capillary supply and a high demand for gaseous interchange. Doubtless many homeostatic mechanisms and enzyme systems are ultimately impaired, and certainly capillary damage plays a role in the pathogenesis of the induced anomalies.[32] An interesting finding by Young[25] was that the body temperature of pregnant animals is lowered almost 10°F. after several hours' stay within the chamber. This raises the possibility that chilling plays an accessory role in the teratogenic processes. Interest has been primarily epidemiologic at the level of populations, and detailed study of the disturbed chemical and physiologic processes brought about by anoxia has not been made. However, further histologic studies of the basic vascular lesion are in progress.

Perhaps the most useful application of the experimental framework is to serve as a model to help shape investigations of the numerous factors that need to be considered and defined in future studies undertaken on human populations. An important finding in this respect is the demonstration of how causation can be determined in retrospect rather than by the ideal method of following up a large series of pregnancies in which many women share a common stress such as influenza or mumps infection. To illustrate, if skeletal anomalies had no relation to anoxic distress and were determined entirely by genetic factors their occurrence would hardly bear any relation to anoxia by week of pregnancy. This is not so: skeletal malformations do occur in significant numbers after anoxic stress during the second week of gestation, and the cause-and-effect relation is reasonably clear. This is essentially the method employed by Gregg in determining the causative relation of rubella in pregnancy to a limited number of specific defects of first-trimester origin.

Although causation can be revealed in retrospect it is also evident from inspection of the data shown in Table 4 — and from the assembled experience on rubella — that causation cannot be proved or risks evaluated except by prospective so-called "follow-up" studies. These risks, so far as anoxia is concerned may be computed from the data given. Even under the controlled conditions of the laboratory it may take years to determine risks whereas in the field, ten years has produced less than 100 reported cases of rubella in pregnancy followed through to the outcome at term.[33] Nevertheless, a beginning has been made both in the laboratory and in the field. Much remains to be learned from experiment, particularly regarding genetic factors and the influence of chronic maternal stress, such as anoxia, anemia or residence at high altitude, on the fetus. Many such studies are underway, and both clinical and epidemiologic data indicate their practical as well as theoretical importance.

Olim and Turner[34] have presented an account of a young woman with congenital heart disease, cyanosis and polycythemia (red-cell count of 5,810,000) on the basis of tetralogy of Fallot who, twice before she was twenty years old, gave birth to an anencephalic infant. After successful operation, cyanosis disappeared, the red-cell count dropped to 4,300,000, and about six months later she became pregnant and a normal living baby was delivered at term.

The adverse effect of high altitude upon health has been the subject of much research and investi-

gation. It is well recognized that in the high plateaus of Peru fertility is greatly depressed and that there is a "timberline" for mammalian reproduction as surely as there is for vegetation. Monge[35] observes that domestic animals brought up to these altitudes 12,000 to 15,000 feet) may not reproduce; he presents the following historical account:

> The well-known historian, Antonio de la Calancha (1639) tells, as does the writer, Martinez Vela, in his "Annals of the Imperial City of Potosi" (4,002 meters above sea level), that when it was first founded there were 100,000 natives and 20,000 Spaniards taken with the fever for riches which made the city so famous. While the former went on reproducing with customary Indian fertility, the latter either did not succeed in having children or they did not survive. The birth of the first Spaniard did not take place until 53 years after the founding of the city.

Indications for further experimental and epidemiologic studies of congenital defects in relation to chronic high altitude are to be found in the clinical impressions of several careful observers. Taylor[36] was impressed with the amount of harelip he was called upon to treat when traveling in upper Nepal, and Limón[37] found tetralogy of Fallot to be unusually rare around Mexico City at an altitude of about 7500 feet though whether this was due to a high case mortality in infancy he was not sure; patent ductus arteriosus, however, was common and observed to run a severe course owing to the development of pulmonary vascular disease seldom observed at sea level.[38] Fragmentary epidemiologic evidence gained from Dr. Victor Alzamora in Lima, Peru (about 500 feet above sea level), points in the same direction, for in the past few years only 8 patients with patent ductus arteriosus who were born in the vicinity of Lima have presented for treatment at a large city hospital in Lima whereas over 30 have been observed in the same hospital who were born at altitudes around or above 10,000 feet.[39]

That such observations are of interest not only to cardiologists but also to pediatricians, obstetricians and public-health workers is abundantly clear and illustrated by the statistical finding of MacMahon[40] that an association with (early) birth rank is demonstrable for patients with patent ductus arteriosus, and this "suggests that the environment influences the incidence of the defect, presumably at the time of birth when the ductus normally closes." On the other hand the finding by Rutstein, Nickerson and Heald[41] that patent ductus arteriosus may be etiologically associated with rubella in the first trimester of pregnancy indicates that failure of the ductus to close may be influenced by events long antedating birth — perhaps by inducing basic deformities of the heart that then result in patency of the ductus. The role of postnatal oxygen sufficiency[42] or insufficiency[43] is more easily demonstrated.

Thus, scattered clinical, epidemiologic and experimental facts are beginning to fall into place like fragments of a jigsaw puzzle, and a vast and intricate design is becoming apparent as the fragments are joined together. The emerging picture is one of many deviations of development caused by timed events of pregnancy that adversely affect the maternal organism. The indications are that neither Neo-Lamarckism nor Mendelian probabilities provide a completely satisfactory explanation of the occurrence of congenital malformations; that environmental factors operate to a far greater degree than was formerly appreciated; that these can be evaluated on a firm scientific basis; and that intelligently conceived measures to protect the fragile embryo or the vulnerable fetus will ultimately be devised.

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MEDICAL INTELLIGENCE

RESUSCITATION OF THE HEART IN VENTRICULAR STANDSTILL BY EXTERNAL ELECTRIC STIMULATION*

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BOSTON

THE purpose of this report is to describe the successful use in 2 patients of a quick, simple, effective and safe method of arousing the heart from ventricular standstill by an artificial, external, electric pacemaker. For the first time it was possible to keep a patient alive during ventricular asystole lasting for hours to days. This procedure may prove valuable in many clinical situations. Cardiac standstill is a serious, usually terminal, event that rarely responds to currently employed therapeutic measures. In patients with complete heart block it may be transient, causing the Stokes-Adams syndrome. Occasionally, cardiac standstill occurs in the absence of heart disease as a terminating accident during peripheral vascular collapse, anesthesia, surgery, trauma, accidental suffocation, drowning or electric shock. Intravenous or intracardiac injections of epinephrine, myocardial stimulation with a needle and direct cardiac massage after emergency thoracotomy have been employed successfully in some cases, but they are intrinsically hazardous and difficult.

In previous experiments on dogs, it was observed that the ventricles could be stimulated by externally applied electric shocks.[1] After a survey of the literature and some preliminary exploratory experiments, a thyratron physiologic stimulator was used to generate periodic impulses of direct current.‡ These were monophasic currents of low voltage, with rectangular shape, 2 to 20 milliseconds in duration and of variable intensity and frequency.

In dogs, with the external electric pulse generator acting as an ectopic ventricular pacemaker, regular, effective ventricular beats were produced when the frequency of stimulation was higher than the spontaneous ventricular rate. When the external electric stimulation was less frequent than the normal cardiac pacemaker, occasional scattered ventricular extrasystoles occurred as the stimuli intermittently reached excitable heart muscle.

Direct application of the stimulating electrodes on ventricular epicardium required minimal current for effective stimulation. However, the necessity for direct cardiac contact of the electrodes has made previous efforts at electric stimulation impractical for clinical purposes.[2, 3] In the early experiments in this laboratory thoracotomy was avoided by the placing of one metal-tipped, insulated electrode in the esophagus at a high ventricular level and the other electrode on or under the skin over the cardiac

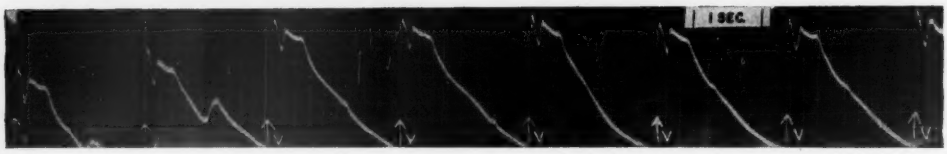

FIGURE 1. *Electrocardiogram (Lead I) Taken during External Electric Stimulation at a Rate of 32 per Minute in Case 1. The moment of electric stimulation is marked by a large, rapid, upward deflection and a wide displacement of the baseline. On all the electrocardiograms the time of electric stimulation is indicated by an arrow, and the ventricular response to it by a "V". A ventricular deflection (broad inverted QRS complex and upright T wave) follows each stimulus regularly, demonstrating the dependence of the ventricular beats on the external electric pulses. P waves of dissociated auricular rhythm are also present.*

*From the Medical Service and Medical Research Department, Yamins Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

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‡Obtained through the kindness of Dr. Otto Krayer.

apex. The position of the electrode in the esophagus was determined by observation of the shape of the auricular and ventricular deflections in esophageal-lead electrocardiograms. In subsequent experiments, stimulating electrodes were attached to needles placed subcutaneously in the chest wall at points in a line traversing the ventricles. The two latter locations of the electrodes permitted quick and easy stimulation of the ventricles with somewhat more intense currents than was necessary with direct contact, but local charring of the tissues did not occur. In several animal experiments the ease, speed and safety of applying electric shocks of this type to subcutaneous needle electrodes and their effectiveness in stimulating the ventricles to beat were repeatedly demonstrated. It was therefore decided to apply this method to the treatment of ventricular standstill in patients.

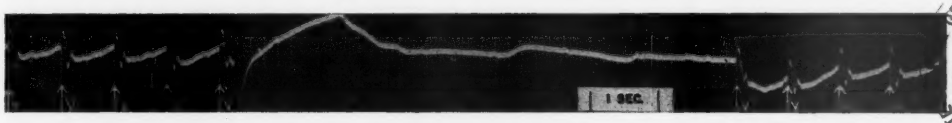

FIGURE 2. *Electrocardiogram (Lead 3) in Case 2, Showing Regular Ventricular Response (V) to Electric Stimulus (Arrow) at a Rate of 78 per Minute, with Intervening Ventricular Asystole When the Stimulator Was Discontinued for Eight Seconds.*

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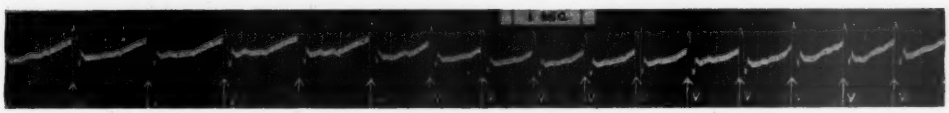

FIGURE 3. *Electrocardiogram (Lead 3) in Case 2, Showing Regular Ventricular Response (V) to Electric Stimulus (Arrow), with Variation in Stimulus Rate from 54 to 78 per Minute.*

CASE REPORTS

CASE 1. D. S. (B.I.H. M33443), a 75-year-old man with complete heart block of 2 years' duration, entered the hospital on August 28, 1952, because of 2 severe Stokes-Adams attacks, which had been treated with intracardiac injections of epinephrine. He showed many cardiac arrhythmias including varying auriculoventricular block, ventricular tachycardia, ventricular beats from varying foci and ventricular standstill. Over a 4-hour period in the hospital 34 intracardiac injections of epinephrine were administered because of repeated cardiac standstill.

Subsequently, external electric stimuli were applied because of more frequent and prolonged episodes of ventricular asystole. The negative electrode of the thyratron stimulator was attached to a needle in the subcutaneous tissue just outside the cardiac apex, and the positive wire was attached to a chest electrode on the skin at the fourth intercostal space in the right mid-axillary line. Electric shocks 2 milliseconds in duration were given at frequencies from 25 to 60 per minute. The intensity of the shocks was increased until ventricular responses were observed.

Cardiac activity was visualized with electrocardiographs and on the rotating fluorescent screen of an attached cardioscope. Ventricular beats regularly followed the electric stimuli by a constant interval (Fig. 1). The rate of the artificial pacemaker was varied purposely to demonstrate that the constant relation of the QRS to the electric shock was one of dependence and not coincidence. Regardless of the state of the ventricles, regular auricular waves continued, but there was always complete dissociation of auricular and ventricular activity. Pulsations were felt in the dorsalis-pedis arteries that regularly followed the stimuli at varying rates.

Recurring, prolonged ventricular standstill could be interrupted by external stimulation over a period of 25 minutes. When the external artificial pacemaker was stopped, idioventricular beats were observed for a brief period before cardiac standstill recurred.

After 25 minutes of intermittent stimulation, however, the spontaneous ventricular electrocardiographic complexes became smaller, more irregular and fewer. The peripheral pulsations and electrocardiographic deflections following electric stimulations disappeared. Another intracardiac injection of epinephrine was followed by ventricular flutter, fibrillation and standstill, but repeated stimulation with external shocks of maximal intensity were ineffective, and the patient died.

At autopsy the pericardium was filled with 600 cc. of blood. Many needle punctures, a large hematoma in the anterior wall of the left ventricle and a puncture in a large coronary vein were observed. Marked cardiac hypertrophy and moderate coronary atherosclerosis were noted.

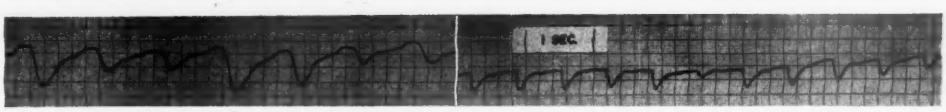

FIGURE 4. *Brachial-Pulse Pressure Tracings in Case 2 at Stimulus Rates of 62 and 90 per Minute. The sensitivity of the electromanometer was varied, so that the size of the deflections is not significant.*

CASE 2. R. A. (B.I.H. M34234), a 65-year-old man, entered the hospital on September 28, 1952, because of increasingly severe congestive heart failure. Severe coronary-artery disease had been present for 8 years. An acute myocardial infarction 6 years previously was followed by increasingly severe and incapacitating angina pectoris and congestive heart failure. Hypothyroidism induced by radioactive-iodine therapy 4½ years previously was associated with marked clinical improvement so that the patient returned to active work. After the onset of complete heart block 5 months before the present admission, angina pectoris and congestive heart failure recurred and became progressively more severe.

During the first few hospital days the ventricular rate was between 30 and 40 beats per minute. At noon on the 6th hospital day, episodes of prolonged asystole with syncope and convulsions began and were treated with 3 intracardiac injections of epinephrine. Prolonged periods of ventricular standstill were then observed alternating with bursts of irregular ventricular complexes from varying foci.

The thyratron stimulator was connected to the patient with hypodermic needles. The negative electrode was attached to a needle in the subcutaneous tissue at the left anterior axillary line in the 5th intercostal space, and the positive electrode was placed at the right anterior axillary line in the 4th intercostal space. Electric shocks at frequencies between 50 and 100 per minute were employed. The intensity of current necessary to produce ventricular beats caused slight contraction of the thoracic muscles, particularly the left pectoral, maintained continuously by the external electric pacemaker for over an hour. During this time, good cerebral function, a blood pressure of 100/70 and strong peripheral pulses at any desired rate were maintained by the stimulator. On repeated short tests of omission of electric stimulation, spontaneous ventricular beats failed to occur; syncope, collapse and apnea supervened, requiring the artificial pacemaker to resuscitate the patient. Subsequently, spontaneous ventricular beats from an intracardiac pacemaker returned for 30 minutes, but at 12:30 p.m., ventricular standstill recurred and the external electric shocks were reapplied. *During the next 52 hours not a single spontaneous ventricular beat was observed.* During this period, until 4:55 p.m. on October 9, the stimulator was the only pacemaker driving the ventricles. It was stopped temporarily every few hours to test for spontaneous beats, but ventricular standstill and syncope always recurred.

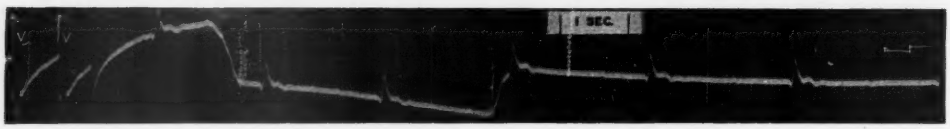

FIGURE 5. *Electrocardiogram (Lead 3) in Case 2, Showing Resumption of Spontaneous Idioventricular Rate and Its Gradual Slowing after Temporary Omission of Artificial Electric Pacemaker (Arrow).*

but was not disturbing to the patient. This adequate stimulus, roughly measured 130 volts at its peak.

Constant ventricular responses to the electric stimuli from the artificial pacemaker were observed in the electrocardiograms. Whenever the external pacemaker was stopped, ventricular standstill immediately recurred or spontaneous idioventricular beats were witnessed (rate of 30 to 45 per minute) for seconds to hours before standstill recurred. Figure 2 shows ventricular standstill when the pacemaker was temporarily discontinued, and Figure 3 ventricular responses to the artificial pacemaker at varying rates. Auricular activity continued at a regular, completely dissociated rate.

The blood pressure was recorded over the brachial artery at frequent intervals. After the initial onset of ventricular asystole on the 6th hospital day, shock appeared, requiring the constant intravenous infusion of nor-epinephrine (Levophed). For the next 8 days, with careful adjustment of the rate of inflow of the nor-epinephrine, as well as the use of the Adequate cerebral function, blood pressure and peripheral circulation were maintained throughout this time by the artificially driven ventricles in addition to the constant intravenous administration of nor-epinephrine.

The optimal artificial ventricular rate was about 90 per minute. At 60 beats per minute, the patient was confused, spoke unintelligibly and showed facial asymmetry and ocular deviations; the blood pressure also tended to drop, and respirations slowed. These changes, which occurred immediately on cessation of stimulation, came on gradually at a stimulus rate of 60 per minute and cleared promptly when the rate was raised to 90 per minute. It is of considerable interest that ventricular rates of 60 per minute produced by the artificial pacemaker were poorly tolerated even for a few minutes, although the patient had tolerated spontaneous idioventricular rhythms of 30 to 40 per minute without difficulty prior to October 4. These observations were made repeatedly, but more precise delimitation of critical ventricular

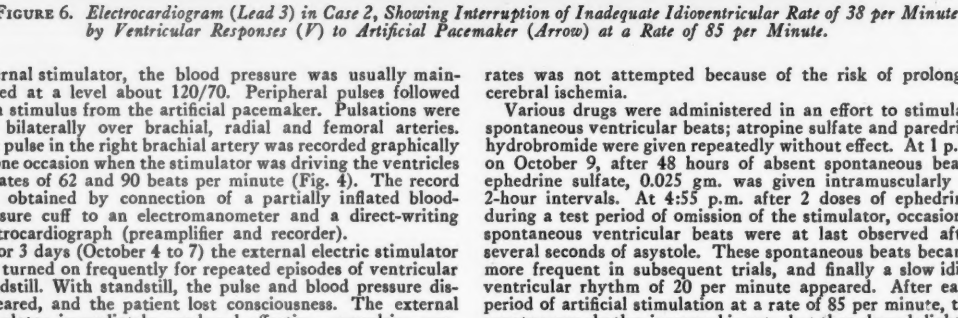

FIGURE 6. *Electrocardiogram (Lead 3) in Case 2, Showing Interruption of Inadequate Idioventricular Rate of 38 per Minute by Ventricular Responses (V) to Artificial Pacemaker (Arrow) at a Rate of 85 per Minute.*

external stimulator, the blood pressure was usually maintained at a level about 120/70. Peripheral pulses followed each stimulus from the artificial pacemaker. Pulsations were felt bilaterally over brachial, radial and femoral arteries. The pulse in the right brachial artery was recorded graphically on one occasion when the stimulator was driving the ventricles at rates of 62 and 90 beats per minute (Fig. 4). The record was obtained by connection of a partially inflated blood-pressure cuff to an electromanometer and a direct-writing electrocardiograph (preamplifier and recorder).

For 3 days (October 4 to 7) the external electric stimulator was turned on frequently for repeated episodes of ventricular standstill. With standstill, the pulse and blood pressure disappeared, and the patient lost consciousness. The external stimulator immediately produced effective, propulsive ventricular beats, with return of peripheral pulses at the rate of the artificial pacemaker and immediate return of blood pressure and consciousness.

On October 7, after 3 days of intermittent external stimulation, spontaneous ventricular beats failed to occur when artificial stimulation was omitted, and the patient had to be rates was not attempted because of the risk of prolonged cerebral ischemia.

Various drugs were administered in an effort to stimulate spontaneous ventricular beats; atropine sulfate and paredrine hydrobromide were given repeatedly without effect. At 1 p.m. on October 9, after 48 hours of absent spontaneous beats, ephedrine sulfate, 0.025 gm. was given intramuscularly at 2-hour intervals. At 4:55 p.m. after 2 doses of ephedrine, during a test period of omission of the stimulator, occasional spontaneous ventricular beats were at last observed after several seconds of asystole. These spontaneous beats became more frequent in subsequent trials, and finally a slow idioventricular rhythm of 20 per minute appeared. After each period of artificial stimulation at a rate of 85 per minute, the spontaneous rhythm increased in rate, but then slowed slightly after several beats, suggesting fatigue of the idioventricular pacemaker (Fig. 5). The more rapid artificial stimulation had to be reinstituted repeatedly, because of the onset of syncope with idioventricular rates of 30 to 38 per minute. Interruption of spontaneous idioventricular rates by the external stimulus at faster speeds was repeatedly observed (Fig. 6).

Finally, at 8 p.m., a persistent spontaneous idioventricular rate of 44 per minute appeared that was adequate to maintain satisfactory cerebral and peripheral blood flow. The electric stimulator was shut off, and adequate cardiovascular function was subsequently maintained with a persistent spontaneous idioventricular rhythm between 30 and 40 beats per minute. No further episodes of syncope or asystole occurred, and the hypodermic electrode needles were removed from the chest 2 days later. The patient's condition improved steadily, and on October 11, his blood pressure remained stable at 110/70 after the administration of nor-epinephrine had finally been discontinued. No neurologic or other ill effects of the 5 days of ventricular standstill and external electric stimulation were evident.

Discussion

In these 2 cases of successful stimulation of the heart in ventricular standstill, 1 patient died of cardiac tamponade resulting from prior repeated intracardiac punctures. Through the use of external electric stimulation applied for five days, the second patient successfully survived repeated episodes of ventricular standstill, one of which lasted fifty-two hours. His heart finally resumed beating without the artificial pacemaker. A simple, effective and apparently safe means is therefore available of arousing the heart from ventricular standstill and keeping it beating until internal pacemakers revive.

The interruption of slow idioventricular rhythm with inadequate cerebral blood flow by a faster, more effective, externally controlled rate, as observed here in man and previously in dogs poisoned with quinidine,[1] suggests other applications of this method. Further clinical and animal experiments are being undertaken to determine the clinical applicability of external cardiac stimulation and to use it as a means for control of heart rates in investigations of cardiovascular dynamics.

Many other problems remain to be explored. The optimal rates of stimulation and the characteristics of the electric pulses in the treatment of ventricular standstill require more experience. The ability to control or produce other types of arrhythmias is also being studied. A simplified pulse generator like the one described by Callaghan[3] might be employed as the electric stimulator for clinical purposes. An additional circuit permitting administration of 110 to 440 volts, 60-cycle alternating current in bursts of 0.1 to 0.2 second as used in animal experiments by Guyton and Satterfield[4] might be added. With such a machine it should be possible to defibrillate the human heart across the unopened chest initially, and then to arouse it from ventricular standstill, maintaining circulation until an orderly, effective spontaneous rhythm reappeared.

Summary

Effective ventricular beats were regularly produced in 2 patients with ventricular standstill after complete heart block by the application of electric stimuli from an artificial, external pacemaker by way of subcutaneous needle electrodes.

The heart was kept beating for twenty-five minutes in 1 patient, who finally died of cardiac tamponade, and for five days in the other, who recovered and ultimately resumed spontaneous idioventricular beats.

In the patient who survived it was possible also to interrupt a slow idioventricular rhythm with a more rapid and effective, externally controlled rhythm.

I am indebted to the medical resident and house officers, Drs. Norman Silberg, Robert Berg, Jerome Fischbein, William Karlen and Louis Mogul, and to the nursing staff, to whose efforts the successful outcome in Case 2 may be credited.

330 Brookline Avenue

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AUSCULTATION OF THE CORRIGAN OR WATER-HAMMER PULSE

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THE Corrigan or water-hammer pulse and the pistol-shot sound in the groin are time-honored physical signs of marked aortic insufficiency. Unmistakable and more serious of the two is the pistol-shot sound in the groin, which means that the diastolic blood-pressure in the femoral artery is 0 and that the aortic insufficiency is extreme.

In current teaching the Corrigan pulse is often misunderstood to mean merely a radial pulse of abnormally large volume; the true Corrigan or "water-hammer" pulse is characterized not only by its large volume but also by the transmission of a sudden shock to the examiner's finger over the radial artery or to the whole hand that is grasping the wrist. A fact that, to my knowledge, has never been reported is that the water-hammer shock represents a pistol-shot sound, which the examiner will hear if he listens with his stethoscope over the radial artery. And it is a further fact that this shock and sound, if absent while the arm rests at body-level, can be made to appear in some cases if the wrist is raised vertically above the heart. This makes possible certain interesting bedside observations.

For it is obvious by simple hydraulics that elevation of the brachial artery to a vertical position from the horizontal will reduce the diastolic pressure at the wrist to a degree measurable, in terms of a vertical column of blood, by the height of the wrist above the heart. Normally, the diastolic pressure is greater than this reduction, so that this arterial tone, which is the same as that used in auscultatory

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taking of blood pressure, does not appear; in certain patients with aortic insufficiency not severe enough to cause the pistol-shot sound in the groin or in the unelevated wrist the diastolic pressure is nevertheless sufficiently lowered not to equal that of a vertical column of blood from heart to wrist, and the tone in the wrist appears.

Thus, in all cases of aortic insufficiency, it is of interest to raise the arm vertically above the heart and to listen to the front of the wrist. If no arterial tone is heard it may be concluded that the insufficiency is not marked and may be slight. If the tone is heard over the elevated wrist but not lower it means a diastolic blood pressure of about 45 by mercurial manometer. This is evidence that the aortic regurgitation has caused a pronounced abnormality of the aortic circulation and, whether or not symptoms of failure of the left ventricle have developed, it is commonly reason for strict limitation of exertion.

Next, with the arm still elevated, it is well to move the stethoscope gradually downward until at some point the tone suddenly disappears. The lower this point, the less the diastolic blood-pressure; if the tone is present as low as the elbow it means a diastolic pressure of about 30.

Obviously, since Corrigan's day, routine determinations of diastolic blood pressure have nullified the importance of his observations. Nevertheless, the appearance of these curious clinical phenomena lends interest to the physical examination.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38461

PRESENTATION OF CASE

First admission. A sixty-five-year-old man was admitted to the hospital because of disorientation and speech difficulty.

For several days before admission the patient was somewhat confused. On the day of admission he spoke slowly, slurred words and used inappropriate words.

He had been known to have hypertension for at least fifteen years. Seven years before admission when he was in the hospital an electrocardiogram showed a recent anterior and an old posterior myocardial infarct. Diabetes mellitus was discovered five years prior to admission and had been controlled by diet alone. He had been taking 0.1 gm. of digitalis daily.

Physical examination revealed drooping of the lower eyelids and a constant right lateral nystagmus. There was weakness of the right facial muscle, slight protrusion of the tongue to the right, very slurred, slow speech and slight weakness of the right arm and hand. The deep tendon reflexes were normal, and the plantar reflexes were flexor. The heart was enlarged, the border extending to the anterior axillary line; no murmurs were heard.

The temperature was 100.3°F., the pulse 70, and the respirations 30. The blood pressure was 170 systolic, 70 diastolic.

The urine had a specific gravity of 1.020 and gave a ++ reaction for albumin and a blue-green sugar reaction. Examination of the blood showed a hemoglobin of 15.1 gm. and a white-cell count of 11,000. The fasting blood sugar was 197 mg. and the nonprotein nitrogen 25 mg. per 100 cc.; the chloride was 99 milliequiv., and the carbon dioxide 31.2 milliequiv. per liter. Lumbar puncture revealed pink, cloudy spinal fluid under a pressure equivalent to 160 mm. of water; the dynamics were normal. The spinal fluid contained 2590 red cells and 4 white cells per cubic millimeter and 128 mg. of protein per 100 cc.

Left temporal burr holes showed no extradural, subdural or remediable intracortical hemorrhage. Postoperatively the patient became comatose and had numerous convulsions, some of which were generalized. His diabetes worsened and required 20 units of insulin daily for control. Then he gradually improved; after thirty days in the hospital he was quite rational, got along well and was discharged.

Second admission (eight months later). Eight days before admission after an enema the patient fainted and fell to the floor. He did not know of any injury to his spine at that time, but later in the evening he experienced pain in the upper lumbar region. The pain was diminished in intensity the next day, but was aggravated by coughing, sneezing or sudden change in position. An x-ray film showed a compression fracture of the third lumbar vertebra.

In the interval since the previous admission he had been quite well. The diabetes had been controlled on diet alone, and there had been no obvious neurologic disability. He had had some shortness of breath on exertion and orthopnea requiring three

pillows for relief, but no chest pain, paroxysmal dyspnea or ankle edema; he had continued to take digitalis.

Physical examination was noncontributory. The urine was normal. Examination of the blood showed a hemoglobin of 13.0 gm. and a white-cell count of 14,600. The fasting blood sugar was 258 mg., the calcium 9.3 mg., the phosphorus 3.0 mg., the alkaline phosphatase 5.3 units and the acid phosphatase 1.6 units per 100 cc. An intravenous pyelogram was normal; all the bones visualized were demineralized, and there was slight wedging of the right lateral margin of the third lumbar vertebra, but no definite osteolytic changes were seen. He was discharged after a week.

Third admission (one year later). The patient's backache had disappeared completely a month after his previous discharge. His main trouble during the interval had been fainting episodes, seven in all, which came on suddenly without any premonition of any sort; during these episodes he remained unconscious for about two minutes, his head and eyes moved to the right, and he had convulsive movements of all his extremities, more severe on the right. On regaining consciousness he felt normal, without residual headaches, drowsiness or stupor. Five days prior to entry when he had one of his usual fainting spells, he fell to the floor, striking his back. On regaining consciousness he noted pain in the upper lumbar region, which persisted and necessitated his being confined to bed, since sitting up or walking about aggravated the pain. Otherwise, his condition had been unchanged except that he had required 20 units of protamine zinc insulin daily for control of the diabetes.

Physical examination was noncontributory. A roentgenogram of the chest demonstrated a coarse strand-like increase in density in the right upper lobe, in the center of which there were two oval radiolucent areas; the heart was grossly enlarged, the aorta tortuous and elongated. X-ray films of the lumbosacral spine showed marked generalized demineralization, with softening of the end plates of the vertebral bodies and protrusion of the intervertebral disks into the vertebral bodies most marked at the level of the third and fourth lumbar vertebras, where there was an associated compression fracture (Fig. 1). X-ray films of the skull showed no increased intracranial pressure; the bones of the vault were demineralized. An electroencephalogram was abnormal, with notably a variety of slow waves; the disturbances were diffuse, but were generally a trifle more marked on the right.

The patient was placed in a cast and was discharged after sixteen days on Dilantin.

Fourth admission (two months later). In the interval the patient had been reasonably well. He had continued to have moderate back pain but had been able to be up and about. He had one seizure, which occurred while he was in bed and had not been preceded by an injury. There had been no fever or weight loss.

The temperature was 98.3°F., the pulse 80, and the respirations 30. The blood pressure was 120 systolic, 60 diastolic.

Examination of the blood showed a hemoglobin of 13.4 gm. and a white-cell count of 11,200, with 66 per cent neutrophils. The nonprotein nitrogen was 20 mg., the total protein 6.5 gm., and the alkaline phosphatase 4.9 units per 100 cc. Examination of a bone-marrow smear was negative. A roentgenogram of the chest demonstrated no great change; several small radiolucencies suggested possible cavitation. In the x-ray films of the spine further

FIGURE 1.

LTURE AND MECHANIC COLLEGE LIBRARY DEC 10 1952 MANHATTAN KANSAS

generalized osteoporosis, as well as what appeared to be frank bone destruction, was noted.

The patient was fitted with posterior body shell-cast and discharged after seventeen days on streptomycin and PAS (para-aminosalycylic acid) therapy.

Final admission (five months later). In the interval he was in the hospital for a short time three months before this admission because of an episode of hematemesis. There was no recurrence of this in the hospital, and the hemoglobin and blood pressure were well maintained. While in the hospital he had a few episodes of what appeared to be auricular fibrillation; an electrocardiogram had revealed an abnormal record without diagnostic pattern. X-ray studies had shown no change. After returning home he received streptomycin, PAS,

digitoxin, Dilantin and 20 units of protamine zinc insulin daily. He had been up and about in a brace and had not had any dyspnea, chest pain, ankle edema, further hematemesis or gastrointestinal symptoms. He had had five convulsive seizures. Four days prior to entry he had another seizure, and on the following day he had excruciating, steady, nonradiating pain in the mid-lumbar spine that was aggravated by any movement of the vertebral column. Although he was unable to move because of the pain, there was no actual paralysis, sensory phenomena or bladder or bowel dysfunction.

Physical examination revealed early diabetic retinopathy, an enlarged heart, spasm of the lumbar musculature and tenderness of the spinous processes of the third and fourth lumbar vertebras.

The temperature was 98.3°F., the pulse 80, and the respirations 20. The blood pressure was 140 systolic, 80 diastolic.

The urine had a specific gravity of 1.020 and was normal. The serum nonprotein nitrogen was 29 mg., and the fasting blood sugar 139 mg. per 100 cc. Roentgenograms of the spine showed the degree of osteoporosis to be more marked and suggested further compression of the first lumbar vertebra.

On the eleventh day the patient vomited several hundred cubic centimeters of dark, coffee-colored material, which gave a ++++ guaiac reaction. Previously, he had apparently had some abdominal discomfort and distention for a few days and diarrhea for three days followed by constipation for two days.

He had not had any significant abdominal pain, and after the vomiting he complained only of slight lower abdominal discomfort. Examination showed partial disorientation, clear lung fields and an irregular heart rhythm at a rate of 116. The abdomen was distended and tympanitic. There was considerable muscle resistance, tenderness and spasm on pressure in the lower abdomen with rebound tenderness and slight costovertebral-angle tenderness. Peristalsis was diminished but audible. Rectal examination showed tenderness in the cul-de-sac. The temperature, respirations and blood pressure were unchanged. The hemoglobin was 15 gm., the hematocrit 56 per cent, and the white-cell count 6500; a stool gave a ++ guaiac reaction. X-ray films of the abdomen showed extensive gastric, small-bowel and large-bowel distention. Gastric aspiration yielded 600 cc. of dark-brown fluid.

He was placed on gastric suction, antibiotics and intravenous therapy. Over the next twenty-four hours the temperature rose to 103°F. and the pulse to 160 (irregular). The abdominal signs became localized to the right side, with spasm, tenderness and rebound tenderness over the whole right half of the abdomen but most marked in the right lower quadrant; peristalsis became inaudible. The suction continued to bring up coffee-grounds material.

On the thirteenth day an operation was performed.

Differential Diagnosis

Dr. Greene Fitzhugh*: I should like to look at the x-ray films.

Dr. Joseph Hanelin: A good many x-ray examinations were done during the years that this man was observed. The first chest examination, approximately nine years before the last admission, shows clear lung fields and an enlarged heart, particularly prominence of the left ventricle. Films of the chest about three years and nine months before the operation demonstrate clear lungs and further cardiac enlargement, chiefly of the left ventricle. In the chest film taken eight months before the operation there is visible on all films, for the first time, changes in the right upper lobe consisting of a strand-like infiltration, in the center of which are two radiolucencies. There is no definite evidence of lymphadenopathy, and the changes as far as we can tell are chiefly within the right-upper-lobe substance. In a film of the chest two months later the lesion in the right upper lobe is about the same.

The skull examinations, three years and six months and again approximately seven months before the operation, fail to show any obvious changes that we might attribute to an intracranial lesion. The pineal gland lies in the midline. There is some calcification of the internal carotid artery as it overlies the sella turcica, without any indication of intracranial aneurysm.

The films of the spine three years and six months before the last admission reveal partial compression of the third lumbar vertebra and some osteoporotic changes. Eight months before the last admission there are considerably more marked osteoporotic changes and greater compression of both the third and fourth lumbar vertebras. The last series of spinal films made several weeks before the operation show further osteoporotic change. We are at no time certain that there was focal destruction although in areas, particularly in the bodies of the third and fourth lumbar vertebras, we wonder about some destruction. The pedicles are preserved, and the cortexes of the vertebras all appear to be intact. In this situation it is hard to differentiate very severe generalized osteoporosis and some diffuse metastatic process, such as myeloma.

Twenty-one months before the last admission, a pyelogram demonstrates normal-appearing kidneys, which concentrate the dye well, and normal calyxes and ureters. The abdominal film taken before the operation shows distention of the stomach and small bowel and some scattered air throughout the large bowel, the distention of the large bowel being proportionately less than that of the rest of the intestinal tract.

Dr. Fitzhugh: Myeloma, I should be inclined to rule out because the serum protein, the bone-marrow biopsy and the blood smears were all

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normal. No Bence-Jones protein was found in the urine.

From the x-ray films the lung lesion would be classified as tuberculosis. It does not look like cancer.

DR. HANELIN: We do not know what the appearance of the lung may have been caused by, but I should favor tuberculosis or some other infectious process.

DR. FITZHUGH: Although examination of the sputum was negative, the patient was put on PAS and streptomycin. The physicians must have believed he had tuberculosis.

This man had a twenty-seven-month story of right-sided neurologic findings, speech difficulty, numerous convulsions soon after the burr holes were done, and 14 convulsions in the following twenty-seven months, more marked on the right side. Lumbar puncture gave a bloody spinal fluid, which I am inclined to assume was not due to a bloody tap but to disease present in the central nervous system. The x-ray films demonstrated compression and other changes in the vertebral bodies that we shall have to evaluate. The patient had osteoporosis, but an elderly man is likely to have osteoporosis. The burr holes gave us no information except negative information. That is sometimes very helpful. The patient must have had some central-nervous-system disease. The convulsions over the next twenty-seven months and the signs that were present on the right side suggest a lesion on the left side of the brain despite the fact that the electroencephalogram showed a probable focus on the right side.

The patient probably had pulmonary tuberculosis; could there have been a tuberculoma of the brain? My colleagues in neurology believe that a patient would not have a history going on for as long as twenty-seven months if he had a tuberculoma. I think the same statement can be made about brain tumor generally although a brain tumor can be quite slow growing and can give a long history.

With the findings here, I do not like to say that this was epilepsy, because right-sided weakness does not occur with epileptic convulsions. I am going to say that the patient had a neoplasm in the brain. There may have been merely marked arteriosclerotic changes, but then how could I explain the bloody cerebrospinal fluid?

Did the patient have a primary silent lesion that metastasized to the brain and then to the vertebras? Were these changes in the vertebras malignant changes? There is a temptation to explain everything by that one diagnosis.

During the final admission he was operated upon, probably for intestinal obstruction. Where was the obstruction? It apparently did not include much of the large bowel. It was probably in the small bowel, in the region of the ileum or in the upper cecum. The white-cell count was 6500 at that time. This was probably an acute process. Appendicitis could have caused all this discomfort. An elderly man can have appendicitis with a white-cell count of 6500, but I do not think this patient had appendicitis.

Did he have a bleeding ulcer? Hematemesis was mentioned before the fourth admission, but was not noted during the final admission. Then he had nausea and vomited coffee-grounds material. If the physicians suspected a bleeding ulcer, I think they would have taken x-ray films of the gastrointestinal tract. However, I think it is unlikely that he had an ulcer because he had no ulcer symptoms, and no real drop in the hemoglobin even when he was vomiting the coffee-grounds material. Did he have esophageal varices? Usually, some red blood is present, and a great deal of hemoglobin is lost. Did he have straightforward diverticulitis? This is usually on the left side of the colon; I think he would have had more abdominal symptoms before the final episode and an elevation of the white-cell count if this had been diverticulitis.

Did he have adhesions secondary to tuberculosis of the peritoneum at some time, followed much later by contraction of the adhesions that caused this obstruction? That is a possibility, but I think not a very likely one. There would have been fluid in the abdomen and some abdominal symptoms during the period that he was observed in the hospital if he had had a tuberculous peritonitis that had caused the final hospitalization. Did he have simple adhesions? Usually, there is a history of a previous abdominal operation.

I shall not go back to the now slightly outmoded approach, in which we used to try to explain everything by one diagnosis. I know that this patient had several diseases — cardiovascular disease, diabetes and pulmonary tuberculosis; in addition, I assume that he had a malignant process somewhere in his body that was not determined by our studies and that he had metastases to the brain and a malignant process causing the obstruction for which he was operated on. My second choice is cerebral disease — again, most probably neoplasm — and a second disease causing the intestinal obstruction, the nature of which I do not know.

DR. GORDON A. DONALDSON: The patient was a very baffling problem when he was on the Medical Service. I saw him the day before he was operated on and could not make a diagnosis. There were so many "red herrings" scattered about that we were loath to operate on him without a fairly clear-cut diagnosis. We thought that the initial ileus might have been due to the fractured spine. It was only after spasm and tenderness had developed in the right lower quadrant, despite the white-cell count of 6500, that we decided to operate on him.

DR. FITZHUGH: Did you make a preoperative diagnosis?

DR. DONALDSON: The anesthetist always insists that we make a diagnosis; it was appendicitis.

DR. ALFRED KRANES: With the pulmonary picture and the actual lesions present, why does Dr. Fitzhugh not consider the possibility of bronchogenic carcinoma?

DR. FITZHUGH: I thought the x-ray picture was so like tuberculosis that he must have that and not bronchogenic carcinoma.

DR. HANELIN: We never could entirely exclude cancer and never can when there is an abnormal density in the lung, but the relatively stationary appearance over a couple of years is somewhat against carcinoma of the lung; it by no means rules it out. Some carcinomas of the lung remain relatively stationary in appearance. Our opinion was that he had an infectious process, most likely tuberculosis.

DR. RICHARD A. FIELD: We followed this man over the week end and originally made the correct diagnosis, but because there were so many discrepancies — the past and present episodes of hematemesis, the normal white-cell count, normal temperature and so forth — we eventually decided that he had an ulcer, with perforation and subacute peritonitis.

CLINICAL DIAGNOSIS

?Acute appendicitis.
?Perforated ulcer with subacute peritonitis.

DR. FITZHUGH'S DIAGNOSES

Cancer of unknown origin, with metastases to brain, ileum and cecum.
Pulmonary tuberculosis.
Arteriosclerotic cardiovascular disease.
Diabetes.

ANATOMICAL DIAGNOSES

Mesenteric-artery embolus, with infarction of ileum, cecum, ascending colon and appendix.
Coronary-artery disease, with myocardial infarct, old, and mural thrombus.
Cerebral infarcts, multiple, old.
Bronchopneumonia.
Pulmonary tuberculosis with cavitation, old.
Osteoporosis.

PATHOLOGICAL DISCUSSION

DR. DONALDSON: At laparotomy the appendix did present itself and was black; we thought we had the solution to the abdominal symptoms as we took out the appendix. During the procedure, it was noted that the appendiceal wall was unusually necrotic, and there was no fecalith that I could feel that might have caused this complete necrosis. Moreover, Dr. T. W. Nielsen, who was assisting, kept remarking about the pungent odor present, which was not unlike that which one detects at the autopsy table. After we had removed the appendix, we explored the small bowel further and found that it presented areas of disease, measuring 2 or 3 cm. long. The bowel wall was covered with a tan membrane that looked much like a diphtheritic membrane. The bowel elsewhere was distended and dusky but seemed to be viable at that time. I do not recall ever having seen such focal areas of necrosis before. Approximately 6 feet proximal to the ileocecal valve these areas terminated, and the bowel above that level, except for the dilatation, was normal.

DR. ROBERT H. FENNELL, JR.: The specimen we received in the Pathology Department consisted of the cecum, ascending colon and approximately 21 feet of adjacent small bowel. The bowel was mottled, with dark-brown areas mingled with black to purple areas. Fibrin was scattered over the serosa. The cecum and appendix showed similar changes but were darker and more friable. The walls of the bowel were thickened and hemorrhagic, and there were small superficial ulcers in the terminal ileum and cecum. A loosely adherent thrombus filled the ileocecal artery. Microscopically, there was infarction of the bowel, and in the small veins of the mesentery there were small thrombi.

The story does not end there, however. Postoperatively, the patient had rales in the chest, had a convulsive seizure and episodes of cyanosis, with tachycardia, developed a very high fever and died on the third day.

At autopsy we found the anastomoses in good condition, and the remaining bowel appeared to have been viable. A thrombus occluded the superior mesenteric artery for 15 cm. The lower portion of the thrombus was adherent but proximally it was more easily dislodged and appeared to have been formed more recently. The portal vein contained a thrombus that extended from the small radicles into the main vessel. The heart was large; it weighed 500 gm. At the apex of the left ventricle the myocardium was thinned and fibrous. This was the scar left from the myocardial infarct that occurred nine years before death. A mural thrombus at the apex was partially organized and appeared to be at least months or years old, but superficially there were layers that were reddish gray and recently formed.

I visualize the sequence of events as follows: an embolus from the apex of the left ventricle lodged in the ileocecal artery, producing infarction of the terminal ileum and causing the first symptoms. This propagated proximally, and also thrombi formed in the veins secondary to the infarction and necrosis. That there were emboli is shown by the multiple small infarcts in the brain, spleen and kidney.

The immediate cause of death was a massive bronchopneumonia involving all lobes. There was an old tuberculous cavity in the right upper lobe, but this was walled off and was unrelated to the bronchopneumonia. There were large numbers of bacteria, cocci and bacilli, in the bronchioles such as we see in the aspiration type of bronchopneumonia.

The bones were osteoporotic, very soft and easily cut. Microscopically, the cortex and trabeculae

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were extremely thin. We were able to see the herniation of the intervertebral disks into the body of the vertebras as was seen on x-ray examination.

Dr. Richardson will tell us about the findings in the central nervous system.

DR. EDWARD P. RICHARDSON, JR.: There was a large lesion in the brain in the left cerebral hemisphere, involving the inferior and middle frontal convolutions and, in part, the superior frontal convolutions. It was characterized by destruction of the cortex and subcortical white matter external to the lenticular nucleus and internal capsule. The internal capsule was somewhat thinner on the diseased than on the normal side. The lesion was typical of cerebral infarction of some months' or years' duration. In addition to the large lesion in the left frontal region there were small lesions of exactly the same nature scattered in both occipital lobes and on the orbital surface of both frontal lobes. These lesions all appeared to be of approximately the same age. They were all typical of cerebral infarction, undoubtedly the result of emboli in this case. There were no recent lesions. In addition, an incidental finding, which does not contribute to the understanding of this case, was a small meningioma, about 1 cm. in diameter, overlying the left frontal lobe nearly beneath the burr hole.

CASE 38462

PRESENTATION OF CASE

A forty-seven-year-old man was admitted to the hospital because of malaise, fatigability, anorexia and weight loss.

Six weeks before entry the patient noted the rather insidious onset of mild, dull epigastric aching unrelated to food intake, defecation or exertion but accompanied by malaise, weakness, anorexia and fatigability. These symptoms gradually increased in severity and for the three or four weeks prior to admission were accompanied by mild fever, weight loss of 10 pounds, nausea, vomiting and a mild, nonproductive cough. A Graham test and a gastrointestinal series were reported as negative. The symptoms persisted, with increasing nausea and vomiting. One week before admission the patient began to experience increasing dull aching pain in the epigastrium associated with definite abdominal tenderness and back pain made worse by motion, jolts or lying on the left side, and relieved somewhat by empirin or by lying on the right side. In addition, for the past week, he had nightly episodes of shaking chills with chattering of the teeth followed by drenching cold sweats. During the day he ran a slight fever. Two days before entry he became so weak that he was unable to get out of bed. He had one light-colored stool, occasional "red" urine but no skin rash, bleeding, hematemesis, jaundice or diarrhea. He had one bowel movement every three or four days.

The patient gave a history of hay fever for ten years, for which he had received injections. He had taken 4 or 5 highballs daily for about twenty-five years but claimed to have had a good diet and denied drunkenness. He also denied any exposure to toxic drugs.

Physical examination revealed a well developed, well nourished man in whom there was questionable scleral icterus but no petechiae, spider angiomas, liver palms or loss of hair. There was a palpable epitrochlear lymph node on the left. The heart and lungs were normal. The upper border of the liver was percussed at the level of the fifth rib, and the inferior border was 5 fingerbreadths below the right costal margin. The edge was sharp, smooth and markedly tender. The spleen was not palpably enlarged.

The temperature was 102.2°F., the pulse 88, and the respirations 14. The blood pressure was 120 systolic, 72 diastolic.

The urine was amber, had a specific gravity of 1.028, gave a negative test for bile and contained 4.0 Ehrlich units per 100 cc. per two-hour specimen of urobilinogen. Its sediment contained 8 red cells per high-power field. Examination of the blood showed a hemoglobin of 11 gm., a red-cell count of 3,700,000 and a white-cell count of 12,400 with 74 per cent neutrophils, 17 per cent lymphocytes, 5 per cent monocytes and 3 per cent eosinophils and 1 per cent atypical monocytes. The hematocrit was 32 per cent, and the sedimentation rate was 61 mm. in one hour. The bromsulfalein retention was 18 per cent, and the cephalin flocculation negative in twenty-four and forty-eight hours. The alkaline phosphatase was 14.7 units, the bilirubin 0.2 mg. direct, 0.2 mg. total, the fasting blood sugar 117 mg., the nonprotein nitrogen 20 mg., the total protein 6.63 gm., the albumin 4.25 gm., the globulin 2.38 gm. with albumin-globulin ratio of 1.8, the cholesterol 218 mg., and the cholesterol esters 140 mg. per 100 cc. The prothrombin time was 14 seconds (normal, 13 seconds). The blood Hinton test, Coombs test, Widal reaction and a test for brucella agglutinins were negative. Two stool specimens were guaiac negative.

A roentgenogram of the chest showed several calcified scars in the right middle lobe. The heart was not enlarged. There was slight elevation of the left leaf of the diaphragm, thought to be due to gas within the stomach and splenic flexure of the colon. A plain film of the abdomen showed considerable enlargement of the liver, with its lower edge at the level of the iliac crest on the right. The kidneys did not appear abnormal except that the upper pole of the right kidney had swung somewhat laterally. The spleen was not grossly enlarged. On barium-enema examination the colon filled readily as far as the cecum without evidence of obstruction.

In the hospital chills persisted, and the temperature ranged from 98 to 103°F. On the fifth hospital day, the blood hemoglobin was 12 gm., and the white-cell count 23,200, with 84 per cent neutrophils, 15 per cent lymphocytes and 1 per cent monocytes. There was a + variation in size of the red cells, and the neutrophils included an occasional band form.

On the ninth hospital day an operation was performed.

Differential Diagnosis

Dr. Perry J. Culver*: This case represents the differential diagnosis of hepatomegaly with fever, anorexia, weight loss and malaise. The initial information about this man made me consider several possibilities: liver disease, either of the parenchymal type or extrahepatic in origin, a chronic infection, carcinoma, lymphoma and sarcoidosis or another granulomatous disease of unknown etiology. The data in the history on which one must try to localize the lesion are pain in the epigastrium, malaise, weakness, anorexia and fatigability, all of which suggest intrahepatic disease possibly of a viral nature. Subsequent liver tests, I believe, ruled out intrahepatic viral disease quite completely. This history of gradual increase in severity of the symptoms over a four-week period and of back pain made worse by motion, by lying on the left side and by jolts makes me wonder about a carcinoma in the region of the pancreas. Another possibility is the development of a septic process in the liver, which could result from external obstruction and which would cause a rapid downhill course with tenderness and pain, but such a process would be less likely to cause pain in the back. The episodes of shaking chills with night sweats suggest that in the week before entry something dramatic happened: perhaps a bacteremia possibly of an *Escherichia coli* origin. And since my attention is now directed to the right upper quadrant, I naturally think of cholangitis of a severe degree or of a liver abscess. The febrile course up to the time of operation bears out that suggestion. The weakness suggests marked progress of debilitating disease or damage to the liver. The one light-colored stool favors obstruction. I do not know whether the "red" urine was due to hematuria, to bile or to urine concentration. I have to take it as a statement from the patient.

*Assistant physician, Massachusetts General Hospital.

Constipation is not a real clue; it could be related to obstructive jaundice or to disease of the pancreas. I do not believe I have to pay much attention to the history of alcoholism since there was no clinical observation to suggest cirrhosis, such as spider angiomas, liver palms or edema; moreover, nothing in the liver-function tests suggested cirrhosis or intrahepatic disease. Apparently, the 4 or 5 highballs daily for twenty-five years caused little clinical damage.

The liver was enlarged on physical examination as nearly as I can tell from the report, but was not nodular, which may or may not be evidence against metastases to the liver. Whenever the liver is greatly enlarged and tender, one thinks of metastatic disease first and then of infection involving the liver.

The laboratory tests I can sum up as follows: there was a leukocytosis, a negative flocculation test, a normal prothrombin time, a normal albumin and an elevated alkaline phosphatase. All these taken together are quite strong evidence against viral hepatitis, cirrhosis or a chronic hepatitis per se. On the other hand they may be strong evidence for a partial obstruction in the biliary tree. One may rightly raise the question of obstruction without jaundice; that particular problem has interested several of us for the last few years. We have seen at least 3 patients who had an elevated alkaline phosphatase, a marked bromsulfalein retention with or without evidence of cholangitis and no clinical jaundice, and yet who at operation showed almost complete obstruction of the common duct from a stone, stricture or tumor. For some reason as yet unknown, almost complete obstruction of a biliary tract occurs occasionally without the development of jaundice. Such a diagnosis warrants serious consideration in this case.

While I am on this subject, I should like to present briefly another idea that has interested us. So far, it is pure theory without facts to support it. The theory is that there may be a differential secretion pressure for the various substances secreted by the liver. Of these, bromsulfalein and alkaline phosphatase may have a lower secretion pressure than bilirubin. Then, in the presence of partial obstruction of the biliary tract with only a slight increase in back pressure, there would be retention of alkaline phosphatase and bromsulfalein in the blood stream, but no increase in the bilirubin level. The liver-function tests in this case suggest that such a partial obstruction in the biliary tree was present.

DR. DANIEL S. ELLIS: Where would you place the obstruction, Dr. Culver?

DR. CULVER: You are getting too far ahead of my train of thought. While I am talking about laboratory tests, I should like to point out several things that would help me in placing the obstruction. I should like to discuss the errors of omission first and those of placement afterward. In deciding about the possible site of an obstructing lesion, I should like to have a stool guaiac test performed. I am not sure whether that test was left out of the record on purpose or whether it was one of those unfortunate cases in which a stool specimen could never be obtained.

DR. BENJAMIN CASTLEMAN: Nothing is left out of the record on purpose. Two stools were examined; they were brown and guaiac negative.

DR. CULVER: Obviously, I am torn between the possibility of carcinoma of the head of the pancreas and partial obstruction without jaundice and a stone in the common duct. If there were a positive stool guaiac test, I should be more inclined to consider carcinoma. It would also be very helpful to have a stool examination for fat and muscle fibers. Many years ago, Dr. Joseph H. Pratt pointed out that if, along with other signs and symptoms, fat and undigested muscle fibers are present in the stool, one can make a diagnosis of pancreatic insufficiency. Also, one clay-colored stool was noted before the patient came into the hospital, and the urinary urobilinogen was extremely elevated on two determinations; therefore, it would be of some help at least academically to know the amount of bile pigments in the stool. If the stool urobilinogens were very much decreased with such marked elevation of urinary urobilinogen, the picture would fit very well with infection caused by an obstruction in the biliary tree. Such an infection would convert the bilirubin in the biliary tree to urobilinogen, which would be reabsorbed and excreted by the kidneys. Then the elevated urinary urobilinogen would not indicate intrahepatic parenchymal disease. A blood culture might have been of interest, but I do not believe it would have changed the situation. I think the increase in the white-cell count was due to an infection in the biliary tree caused by the obstruction.

Finally, I come to the operation. There are three possible operations: the first is a biopsy of the liver, but I do not believe that such a procedure was indicated or would have been done in this case; the second is a biopsy of the lymph node in the elbow, but it also does not seem indicated here; the final possibility is an exploratory laparotomy, which I suspect was performed. At exploratory laparotomy the question to be settled was whether there was an obstruction of the common duct or of the ampulla of Vater by a stone, or a carcinoma of the pancreas.

May I look at the x-ray films, which may give me some clue to that?

DR. STANLEY M. WYMAN: These films were selected from the Graham test and show a normal-appearing gall bladder. The hepatic enlargement is quite well demonstrated. Unfortunately, the films of the gastrointestinal tract are overpenetrated, and the point I should like to know about — namely, the contour of the duodenal loop — is beyond my vision; I cannot call it normal or abnormal from the film. Otherwise, the visualized portions of the upper gastrointestinal tract are not remarkable. The spleen is too poorly outlined for comment. The chest shows no active disease. The scarring described is shown in these small areas of calcification; I think they are of no clinical importance.

DR. CULVER: Can you see the right kidney?

DR. WYMAN: The right kidney seems to lie a little farther laterally in its upper portion than in its lower, most probably because of inward displacement of the lower pole by the enlarged liver rather than outward displacement of the upper pole. In this film one might wonder about splenic enlargement, but I do not think the enlargement is sufficiently definite for one to be positive.

DR. CULVER: In conclusion, the differential diagnosis lies between stone obstructing the common duct and carcinoma of the pancreas. In favor of stone is cholangitis, which is much more frequently associated with stone than with carcinoma. Against stone is the fact that this patient had a short and rapidly progressive downhill course and apparently had been very sick. In conclusion, I shall say that the patient had a carcinoma of the pancreas, with cholangitis.

DR. FARAHE MALOOF: Could this man have had metastatic disease of the liver without obstruction of the common duct?

DR. CULVER: Yes, although with metastatic carcinoma I have often seen changes in the cephalin-flocculation test.

DR. ELLIS: Why was the liver large?

DR. CULVER: Because of the cholangitis.

DR. ELLIS: Why was he not jaundiced if he had a cholangitis? It is not reasonable to ascribe hepatomegaly of this degree to cholangitis in the absence of jaundice.

DR. CULVER: I had such a patient a year ago.

DR. ALFRED KRANES: I, like Dr. Ellis, am inclined to disagree with Dr. Culver's conclusions. I find little evidence of obstruction. Although it is true that a very rare patient with biliary obstruction may not be jaundiced, that is a most unusual situation. The clinical findings and the laboratory tests are equally consistent with some sort of malignant lesion of the liver — metastatic or primary.

A PHYSICIAN: Were both lobes of the liver enlarged?

DR. ELLIS: The liver was tremendous and was felt on both sides of the midline.

DR. KRANES: That would argue against any significant degree of obstruction of the extrahepatic biliary tract.

DR. CULVER: Not completely, but it would be in favor of a metastatic lesion of the liver; I shall stick to a diagnosis of carcinoma of the head of the pancreas producing bile-duct obstruction.

DR. ELLIS: When I first saw this patient, my thought was that the entire picture was more suggestive of neoplasm than anything else; the fever, the hepatomegaly and palpable axillary and inguinal lymph nodes suggested lymphoma. The tenderness of the liver suggested hepatitis; however, with hepatitis causing this degree of hepatomegaly I should expect more abnormality of the liver-function tests. I thought an easy way to find out would be to do a liver biopsy and recommended that that be done. My diagnosis was lymphoma or metastatic carcinoma of the liver, with hepatitis as the last choice. There was no evidence of obstruction that could be detected clinically at any time up to that point.

CLINICAL DIAGNOSIS

Lymphoma or metastatic carcinoma of liver.

DR. CULVER'S DIAGNOSIS

Carcinoma of head of pancreas, with extrahepatic biliary-tract obstruction and cholangitis.

ANATOMICAL DIAGNOSIS

Carcinoma of tail of pancreas, with metastases to liver.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: With that in mind Dr. Ellis got out the long needle that he uses to aspirate the liver and took a biopsy. This proved to be a perfectly normal section of liver except for a tiny spot composed of atypical cells that certainly looked like cancer cells. We believed that these cells were probably metastatic carcinoma although the island of cells was too small for us to be sure it was not a primary liver-cell carcinoma; yet the liver tissue around the collection of neoplastic cells was normal, not cirrhotic, and therefore it was unlikely to be a hepatoma. There was no evidence of bile stasis to indicate extrahepatic obstruction.

The physicians who were taking care of the patient wished a more definite diagnosis and had him explored. A tremendous liver full of metastatic carcinoma was found. Apparently, Dr. Ellis's needle just scraped the edge of a metastatic nodule. The surgeon was able to feel an obvious neoplasm in the tail of the pancreas, which would certainly account for the severe back pain, which the patient experienced especially when he moved.

DR. CULVER: What about the ampulla?

DR. CASTLEMAN: That was not examined, but if there had been any degree of cholangitis, we should have been able to see it in the liver biopsy.

DR. ELLIS: The common duct and gall bladder were perfectly normal.

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ELECTRIC STIMULATION IN CARDIAC ARREST

ONE of the most distressing emergencies confronting the physician is sudden cardiac arrest. Although usually a terminal event in badly diseased hearts, cardiac arrest also occurs unexpectedly in patients with normal hearts during vascular collapse, surgery, anesthesia, trauma, drowning, suffocation and electric shock. Currently employed therapeutic measures must be applied promptly, are successful only occasionally and are intrinsically hazardous and difficult. Although it is a most formidable procedure, open thoracotomy and manual massage of the heart is often resorted to at present.

It has long been known from experience with lightning and accidental electrocution that electric current applied externally may have a profound effect upon the heartbeat. It is also well established that ventricular fibrillation may be stopped and auricular or ventricular contractions may be stimulated by direct application to the heart of electric impulses of the proper type.[1-3] The necessity for direct contact of electrodes with the heart has made these methods of electric stimulation impractical for general clinical use. Cardiac resuscitation by a quick, easy and safe method of external application of electric current across the unopened chest has not hitherto been practicable.

An exceedingly promising report by Zoll in this issue of the *Journal* describes the successful stimulation of the heart in 2 patients with complete heart block and cardiac arrest due to ventricular standstill. External electric stimulation applied by way of subcutaneous needle electrodes was clearly successful in restoring effective ventricular contractions. In 1 patient the heart was kept beating continuously by the artificial pacemaker over a fifty-two-hour period of persistent ventricular standstill. The efficacy of external stimulation was repeatedly evidenced by asystole and lapse into unconsciousness whenever the electric stimulator was turned off. Subsequently, in the clinical course of the same patient, a slow, inadequate idioventricular rhythm was replaced with a faster, more effective, externally controlled rate. More extensive experience will indicate the regularity with which such external control of ventricular rate can be achieved.

As the author points out, successful treatment of ventricular fibrillation may also become feasible by this method of external electric stimulation across the unopened chest: first by defibrillating the heart and then by producing ventricular beats until an orderly, effective spontaneous rhythm reappears. The applicability of the procedure to cardiac standstill during operations, during the course of acute myocardial infarction and in other emergency situations presents interesting possibilities that will surely be explored by many investigators.

The restoration of life in the second patient exemplifies the rapid advances being made in the treatment of cardiac disease. Four and a half years before admission the patient had been bed ridden, with severe congestive heart failure and angina pectoris. The administration of a new therapeutic agent, radioactive iodine,[4] made it possible for him

to be comfortable for three and a half years and even to engage in gainful work. His survival during the episode of cardiac standstill described was accomplished by the concomitant intravenous administration of nor-epinephrine[5] to combat vascular collapse. Thus, three striking therapeutic measures of recent origin were used simultaneously to achieve this successful result.

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PATHOLOGY AND THE SCIENTIFIC EXHIBIT

It is believed that the oldest existing pathological society in the world is the New York Pathological Society, founded in 1844. This medical organization antedates not only the New York Academy of Medicine by several years but also the American Medical Association. The Société Anatomique was formed in Paris in 1803 but lasted only five years, although it was revived in 1826. A pathological society was formed in Philadelphia in 1839, but it, too, expired after a brief life of only four years. Except for the New York society, pathology does not appear to have been organized as a specialty until 1900, when the American Association of Pathologists and Bacteriologists was formed, to be followed by the Pathological Society of Great Britain and Ireland in 1906, the American Society of Experimental Pathology in 1913 and the American Society of Clinical Pathology in 1922.

The revival of interest in 1900 coincided with the first Scientific Exhibit of the American Medical Association, held in 1899. The lone exhibitor was a pathologist, Frank B. Wynn, of Indianapolis, who showed specimens, with proper case histories. Dr. Wynn's initiative was richly rewarded, for the Scientific Exhibit, as it is known today, is one of the outstanding features of an annual meeting of the American Medical Association, and pathology is frequently the central core around which the whole exhibition is planned.

The Wynn exhibit in 1899 was the natural sequence of his prior activities. The Indianapolis Medical Society, beginning about 1895, held a "case history" night once a month, which gradually developed into a "pathologic specimen" night. One of the leaders in this movement was Dr. Wynn, a teacher in pathology at the Medical College of Indiana (later to become Indiana University College of Medicine). During the course of several years Dr. Wynn amassed a sizeable collection of specimens. When the Indiana State Medical Society held its fiftieth anniversary in Indianapolis in 1899, Dr. Wynn, at the urging of William N. Wishard, was encouraged to arrange an exhibit of his specimens. The response was so enthusiastic that the state medical society voted to send the collection to Columbus, Ohio, for the American Medical Association meeting the following week.

Dr. Wynn was doubtful about the advisability of the venture because "nothing like it had ever been done before." However, a vacant store across from the Capitol building in Columbus was rented, shelves and benches installed, and more than 700 specimens shown. (Whether all these specimens were from Dr. Wynn's collection at the Medical School, or whether there were other contributors is not known.)

In 1900, W. W. Keen, president of the American Medical Association, appointed two "unofficial" committees — one to form a new section on pathology and the other to organize a pathology exhibit. Dr. Wynn was secretary of both groups. The exhibit was shown in the same room where the Section held its meetings.

In 1902, when Dr. Wynn was chairman of the Section on Pathology and Bacteriology, his chairman's address was devoted largely to the future of the Pathology Exhibit. Among other recommendations he suggested that the name be changed to Scientific Exhibit, the scope be broadened to include all medicine, the work be placed in entire charge of a director, and the director, in conjunction with the Section officers, correlate the work of the Scientific Exhibit with the work of the various sections.

Awards were given in the Scientific Exhibit of the American Medical Association beginning in 1908, the first gold medal going to Howard R. Ricketts for his exhibit on tick fever.[1]

But the New York Pathological Society is the sturdy ancestor of much of the advance in this

special field of medicine. Among the founders in 1844 were Lewis A. Sayre, Willard Parker, Alonzo Clark and James R. Wood. Later came Francis Carter Wood, James Ewing, Francis Delafield, T. Mitchell Prudden and many others of national and international fame. Notes of the meetings as early as 1847 have been preserved and have recently been reproduced.[2]

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THE STUDY OF CONGENITAL ANOMALIES

The Medical Progress report by Ingalls and his associates in this issue of the *Journal* is an extension of preliminary work published two years ago in *The American Journal of Diseases of Children*.[1] It presents the current record of almost five years of experimentation. Using anoxia as a teratogenic agent, the Harvard group has undertaken a systematic evaluation of both dosage factor and time factor in relation to maternal stress leading to congenital anomalies.

Enough work has been done to show that the mouse is as useful in the study of acquired congenital defects as the rat in that of the human problem of rickets or the guinea pig in that of scurvy. Certainly, the induction of such skeletal defects as hemivertebra, fused ribs and cleft palate and anomalies involving the soft tissues on a predictable basis opens the way to an intensive study of causation. An evaluation of both hereditary and environmental influences is made possible.

Within the framework of the experimental model presented, future consideration will doubtless be given to the subject of chronic as opposed to acute anoxic stress. Both clinical and epidemiologic data indicate the practical as well as the theoretical importance of such investigations.

Olim and Turner[2] have described the course of a young woman suffering from congenital heart disease of unknown cause. She was cyanotic, had a red-cell count of 5,810,000 and showed clubbing of the fingers; the diagnosis of tetralogy of Fallot was made. On two occasions before she was twenty years of age she was delivered at about the sixth month of gestation of a congenitally malformed (anencephalic) infant. After operation, at which a Blalock procedure was carried out, evidence of anoxia disappeared. Cyanosis changed to normal color, the red-cell count dropped to 4,300,000, and the patient stated that she was leading a normal life and was able to walk several miles in a day. About six months after operation she again became pregnant and came to term with a normal baby that presented no congenital abnormalities.

The potential ability of chronic anoxia to cause mass injury of the unborn population is most readily studied in the Alps, the Himalayas and the Andes, although methodical epidemiologic investigations are barely underway. However, it is well known that in the "alto planos" of Peru fertility is greatly depressed and that there is a timberline for mammalian reproduction as surely as there is for vegetation. Monge[3] writes that domestic animals brought up to these altitudes (about 18,000 feet) will not reproduce and reports historically that it was fifty-three years before the first Spanish child was born in Potosi, a city situated at an altitude of about 4000 meters and numbering approximately 20,000 Spanish inhabitants in the seventeenth century. Apart from life and death as related to chronic anoxia the matter involves congenital deformities. Observation of a hospital population in Lima suggests that persons suffering from patent ductus arteriosus are more commonly born at altitudes around 3000 meters than in the vicinity of Lima, which is about 500 feet above sea level.

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DIABETES COMMITTEE OF THE HEALTH COUNCIL

In line with the seasonal interest in diabetes detection associated with the annual Diabetes Week, sponsored by the American Diabetes Association each fall, and the concurrent Diabetes Fair of the New England Diabetes Association, another organizational activity is worthy of mention.

This is the establishment of a diabetes committee of the Health Council of United Community Services of Metropolitan Boston, which has held its first meeting this fall. Serving as a central planning committee of approximately thirty members, the new group "will attempt to determine areas of greatest need in the present and future diabetes

problem; to promote effective measures and facilities to meet the needs; and to encourage coordination of various organizations already carrying on diabetes activities."

The Health Council is by such action functioning according to the principles that have motivated it from the beginning and that it inherited from its progenitor, the Boston Health League. These are to study community needs in any given direction, to plan ways in which these needs may be met, and to advise existing agencies in their fulfillment.

The fee of a Spanish physician at present is said to be twopence from a tradesman, tenpence from a man of rank, and nothing from the poor. In France the fee from a tradesman is from three to five francs; from a man of rank and wealth, much higher.

Boston M. & S. J., *November 17, 1852*

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NONCLINICAL NOTES

Dr. Hugh R. Leavell, professor of public-health practice at the Harvard School of Public Health and a member of the editorial board of the *Journal*, has become president-elect of the American Public Health Association.

CORRESPONDENCE

FOREIGN "EXPERTS"

To the Editor: I received recently a package of issues of the *Journal* and read them with my usual interest. But most of all, I found the editorial on foreign experts most to the point and close to my heart.

I am one of the many "experts" assigned to foreign countries who have not had any training at all in the field of public health or any experience in that field. Still, I am styled an expert and as such am one of about 25 imposters supposedly aiding and advising colleagues in underdeveloped countries. Frankly, I am often quite ashamed of the part I have to play in the farce, which should really be a beautiful display of efficiency and good-will.

It is bad enough that present programs are inefficient and somewhat deceptive, but their very inadequacy may defeat the diplomatic mission for which this aid was designed — the gaining of friends and strength in the underdeveloped countries. The Asian is brought up to respect the aged and learned; he rejects the green novice who comes to advise him because by accepting advice from an untrained person he acknowledges the novice to be superior to himself (and he might therefore lose face); or he may ignore and privately abuse the effort made, ignoring the parts that may be of value because the bad taste of the deception remains.

It is hoped that editorials such as yours will awaken the planners and program makers in Washington to their moral obligation in their work. Sending experts who are truly experts will win respect and friends and gratitude; sending amateurs detracts from the good intentions of the American people and can only make them lose face.

Note: The name of the author of the above letter is withheld for obvious reasons. — ED.

BOOK REVIEW

The Cyclopedia of Medicine, Surgery, Specialties. Edited by George M. Piersol, M.D., and Edward L. Bortz, M.D. 14 vol. and index. 8°, bound. Philadelphia: F. A. Davis Company, 1952. Set $195. Annual revision pages, $15. Review service, $10. (Sold only by subscription.)

This standard cyclopedia has been published for more than twenty years and has gone through a number of editions. This edition is issued in a new format of the loose-leaf type, and it is planned to keep the material up to date by annual revisions of the text and by a supplementary review service. The text is not run solid as in previous issues, but each article heads a new page and is signed by its author. The editors are assisted by 6 chief associate editors and a large corps of associate editors, representing the various fields of medicine and surgery. The text has been thoroughly revised and in some cases rewritten in accordance with the latest advances in medicine, surgery and other specialties. Emphasis has been placed on treatment. The arrangement is alphabetical by subjects, making for rapid and convenient use. References to the literature have been limited, when used, to recent and important contributions. Each article is written by an authority on his subject.

The publishing is excellent in every way, the type is particularly good, and the illustrations adequate. Each volume has about 1000 pages of two-column material. The work, which forms a complete, compact, ready-to-hand reference source for the busy practitioner, is a library in itself, and should prove valuable for rapid consultation.

JAMES F. BALLARD

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Doctor Under Three Flags. By Fannie Anderson. 8°, cloth, 185 pp. Detroit: Wayne University Press, 1951. $3.50.

Mrs. Anderson relates the medical history of Detroit, Michigan, from 1701 to 1837, under French, British and American flags. The text is divided into five parts: French, 1701–1760; British, 1760–1783; the interim between two wars, 1783–1812; the war of 1812 and its aftermath, 1812–1817; and the doctor in the Territory of Michigan (U. S. A.), 1817-1837. Each of the parts is well documented with extensive notes, and there is an extensive bibliography of sixteen pages. The lack of an index detracts from the reference value of the book.

Urine and the Urinary Sediment: A practical manual and atlas. By Richard W. Lippman, M.D., research associate, Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, California. 8°, cloth, 124 pp., with 61 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $7.50.

This monograph is designed to serve as a practical guide in the examination of urine and the urinary sediment. The illustrations are made from colored photographs. The text is divided into three chapters: proteinuria and elements of the urinary sediments; observations on the urine in disease; and general considerations and technic. A bibliography is appended to the text, and there is a good index.

NOTICES

NEW ENGLAND RHEUMATISM SOCIETY

The fall meeting of the New England Rheumatism Society will be held in Sherman Auditorium, Beth Israel Hospital, 330 Brookline Avenue, Boston, on Thursday, November 20, at 8:15 p.m.

PROGRAM

The Challenge of Rheumatic Fever Today. Dr. T. Duckett Jones.

The Present Status of Hormone Therapy in Rheumatic Fever. Dr. David Rutstein.

A discussion period will follow. Questions should be submitted in writing to Dr. Robert Talkov at Beth Israel Hospital.

COMBINED ANESTHESIA TEACHING CONFERENCES OF BOSTON

Programs for the Combined Anesthesia Teaching Conferences during November, December and January are as follows:

November 18. Meeting in conjunction with Massachusetts Society of Anesthesiologists.

November 28 (chairman, Dr. Arrowood). Pain Mechanisms: role of anesthesiologist in management of pain problems; organization of pain clinic.

December 5. Meeting in conjunction with New England Society of Anesthesiologists.

December 12 (chairman, Dr. Hand). Anesthesia for Thoracic Surgery: factors determining choice of agents and methods; anesthesia technics; special physiologic problems.

December 19 (chairman, Dr. Wiggin). Inhalation Therapy (Indications, Methods of Administration, Equipment): methods of artificial ventilation (mechanical resuscitators; manual methods).

January 2. Meeting of Massachusetts Society of Anesthesiologists.

January 9 (chairman, Dr. Etsten). Problems of Anesthesia for Patients with Pulmonary Disease: pulmonary-function studies.

January 16 (chairman, Dr. Smith). Anesthesia for Infants and Children: special characteristics; premedication; choice of anesthesia; complications.

January 23 (chairman, Dr. Arrowood). Anesthesia for Patients with Cardiac Disease: electrocardiograms in surgical patients; use of pharmacologic agents in preparation for surgery; in emergency situations).

January 30 (chairman, Dr. Derrick): Problems of Anesthesia in Surgery of the Heart and Great Vessels: pathologic physiology; control of cardiac arrhythmias; respiratory assistance.

These meetings are held in the auditorium of the Evans Memorial of the Massachusetts Memorial Hospitals, 750 Harrison Avenue, Boston, on Friday evenings, from 7 to 9 o'clock, except when they are in conjunction with the anesthesia societies.

All physicians are invited to attend.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

A regular meeting of the New England Society of Physical Medicine will be held at the Veterans Administration Hospital, South Huntington Avenue and Heath Street, Boston, on Wednesday, November 19, at 7:30 p.m.

PROGRAM

7:30 p.m. Inspection of Physical Medicine and Rehabilitation Service.
Paul D. Faden, B.B.A., Executive assistant.

SECTION CHIEFS

Alfred B. Ellison, B. S., Corrective Therapy
Virginia M. Greenwood, B.S., R.P.T., Physical Therapy
Timothy Keane, Manual Arts Therapy
Francis O'Meara, B.S., Ed.M., Educational Therapy
L. Ruth Steglich, O.T.R., Occupational Therapy

8:00 p.m. Welcome. Dr. George P. Denny, manager, Veterans Administration Hospital, Boston.
The First International Congress of Physical Medicine (illustrated with colored slides). Dr. Sidney Licht.
Collation.

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, November 18, at 12 noon.

Dr. Jack R. Ewalt, Massachusetts Commissioner of Mental Health, and clinical professor of psychiatry, Harvard Medical School, will speak on the subject "The Role of the General Practitioner in the Mental Health Program." Physicians are cordially invited to attend.

NEW ENGLAND OTO-LARYNGOLOGICAL SOCIETY

The afternoon meeting of the New England Oto-Laryngological Society will be held in the auditorium of Boston University School of Medicine, 80 East Concord Street, Boston, on Wednesday, November 19, at 2 o'clock.

PROGRAM

Introduction. Dr. Leighton F. Johnson.

Surgery of the Sympathetic for Ménière's Disease, Tinnitus and Nerve Deafness. Mr. E. R. Garnett Passe, F.R.C.S., of London, England (owing to his untimely death his work is presented by Mrs. E. R. Garnett Passe, of London, England).

Discussers:

The Development of Surgery of the Sympathetic Nervous System. Dr. Reginald H. Smithwick (by invitation).

Theoretical Aspects of Dorsal Sympathectomy in Labyrinthian Lesions. Dr. Derek Denny-Brown (by invitation).

The Use of Stellate Ganglion Block in Selection of Cases for Dorsal Sympathectomy. Dr. George P. Whitelaw (by invitation).

Three Cases of Neurovascular Disease of Labyrinth Treated by Unilateral Dorsal Sympathectomy. Dr. M. Stuart Strong (by invitation).

Closing Remarks. Dr. Leighton F. Johnson.

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NATIONAL FOUNDATION FOR INFANTILE PARALYSIS POSTDOCTORAL FELLOWSHIPS

The National Foundation for Infantile Paralysis announces the availability of a limited number of postdoctoral fellowships in the field of public health and preventive medicine. The purpose of these fellowships is to prepare physicians to fill the many vacancies existing in public health and preventive medicine, with priority to those who are interested in entering the teaching field.

The fellowships are for one or more years at an approved school of public health, with a period of field experience when arranged by the school. Stipends to fellows are based on the individual need of each applicant. Fellowships may cover tuition, maintenance and an allowance for books, if required. An appropriation of $330,600 in March of Dimes funds has been made to cover the cost of the program.

Eligibility requirements include United States citizenship, sound health, graduation from an approved school of medicine and completion of at least a one-year internship in an approved hospital. Selection of candidates will be made on a competitive basis by a clinical fellowship committee composed of leaders in the field of medicine and professional education.

Complete information concerning qualifications and applications may be obtained from the Division of Professional Education, National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York.

LABORATORY REFRESHER TRAINING COURSES

A series of Laboratory Refresher Training Courses will be given in the Communicable Disease Center, Chamblee, Georgia, January–December, 1953.

Information and application forms may be obtained from Laboratory Training Services, Communicable Disease Center, United States Public Health Service, P. O. Box 185, Chamblee, Georgia.

ANNUAL CONGRESS ON MEDICAL EDUCATION AND LICENSURE

The forty-ninth annual congress on Medical Education and Licensure, conducted under the auspices of the Council on Medical Education and Hospitals of the American Medical Association and the Federation of State Medical Boards of the United States, will be held in the Red Lacquer Room, Palmer House, Chicago, on Monday and Tuesday, February 9 and 10, 1953.

In addition, an open meeting of the Advisory Board for Medical Specialties will be held at the Palmer House immediately before the Congress on Sunday, February 8, from 9:00 a.m. to 12:30 p.m.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 6–DECEMBER 8 AND MARCH 2–MAY 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

OCTOBER 7–DECEMBER 9. Massachusetts Department of Mental Health. Course in Child Psychiatry (Pediatric Neuropsychiatry). Page 540, issue of October 2.

NOVEMBER 14–29. Springfield Hospital Educational Program. Page 623, issue of October 16.

NOVEMBER 14 AND 15. Diabetes Fair. Page 623, issue of October 16.

NOVEMBER 17. New England Cardiovascular Society. Page 698, issue of October 30.

NOVEMBER 17–19. Association of Military Surgeons of the United States. Page 583, issue of October 9.

NOVEMBER 17–MARCH 23. Postgraduate Course in General Medicine. Page 697, issue of October 30.

NOVEMBER 18. South End Medical Club. Page 785.

NOVEMBER 18–January 30. Combined Anesthesia Teaching Conferences of Boston. Page 785.

NOVEMBER 18, FEBRUARY 6 AND APRIL 3. New England Society of Anesthesiologists. Page 418, issue of September 11.

NOVEMBER 19. New England Center Hospital House Officers' Association. Page 661, issue of October 23.

NOVEMBER 19. E. Stanley Emery Memorial Lecture. Page 662, issue of October 23.

NOVEMBER 19. New England Conferences on Allergy and Related Subjects. Page 697, issue of October 30.

NOVEMBER 19. New England Society of Physical Medicine. Page 785.

NOVEMBER 19. New England Oto-Laryngological Society. Page 785.

NOVEMBER 19–DECEMBER 17. Lahey Clinic Lectures. Page 698, issue of October 30.

NOVEMBER 20. New England Rheumatism Society. Page 785.

NOVEMBER 21. New York Tuberculosis and Health Association. Page 583, issue of October 9.

NOVEMBER 25. Norfolk District Medical Society. Page 583, issue of October 9.

NOVEMBER 26–APRIL 8. Postgraduate Medical Institute. Page 452, issue of September 18.

DECEMBER 2. Lecture on Cancer Research. Page 697, issue of October 30.

DECEMBER 10–13. New York State Society of Anesthesiologists. Page 744, issue of November 6.

DECEMBER 12 AND 13. Association for Research in Nervous and Mental Disease. Page 584, issue of October 9.

DECEMBER 15–17. American Academy of Obstetrics and Gynecology. Page 744, issue of November 6.

JANUARY 14, 1953. Essex North District Medical Society. Page 743, issue of November 6.

FEBRUARY 9 AND 10. Annual Congress on Medical Education and Licensure. Notice above.

MARCH 16–27 AND NOVEMBER 16–27. Courses in Laboratory Diagnosis of Tuberculosis. Page 744, issue of November 6.

MARCH 30–APRIL 3 AND NOVEMBER 9–13. Courses for Laboratory Directors, Senior Laboratory Staff Members and Physicians. Page 744, issue of November 6.

MAY 13. Essex North District Medical Society. Page 743, issue of November 6.

MAY 19–21. Massachusetts Medical Society. Hotel Statler, Boston.

MAY 28. American College of Chest Physicians. Page 743, issue of November 6.

AUGUST 24–28. Eighth International Congress on Rheumatic Diseases. Page 584, issue of October 9.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

JANUARY 14. Pentucket Club. 111 Main Street, Haverhill.

MAY 13. Andover Country Club, Shawsheen.

MIDDLESEX WEST

NOVEMBER 17–MARCH 23. Postgraduate Course in General Medicine.

NORFOLK

NOVEMBER 25. 8:00 p.m. John Ware Hall, Boston Medical Library.

JANUARY 27.

FEBRUARY 24.

MARCH 24.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNIN THURSDAY, NOVEMBER 20

THURSDAY, NOVEMBER 20

*8:30–10:00 a.m. Orthopedic Staff Conference, Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Peptic ulcer. Dr. Reginald H. Smithwick. Stearns Auditorium, New England Center Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.
*7:30 p.m. Interpretation of Electrocardiograms. Lectures and Demonstration given by Drs. E. E. Hinton, C. C. Bailey and Walter Goodale. New England Deaconess Hospital.
8:15 p.m. New England Rheumatism Society. Sherman Auditorium, Beth Israel Hospital.

FRIDAY, NOVEMBER 21

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Dr. Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
10:30 a.m.–1:30 p.m. Combined Medical and Surgical Rounds. Stearns Auditorium, New England Center Hospital.
11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.
*7:00–9:00 p.m. Combined Anesthesia Teaching Conferences of Boston. Amphitheater, Evans Memorial, Massachusetts Memorial Hospitals, Eighth Floor, 65 East Newton Street.

SATURDAY, NOVEMBER 22

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, NOVEMBER 24

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Hematology Conference. Dr. Dameshek. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*2:00–8:30 p.m. Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital, Waltham.
5:15 p.m. Staff Meeting. Harris Hall. New England Deaconess Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, NOVEMBER 25

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Tumor Clinic. Discusser, Dr. Eugene Stead. Pratt Diagnostic Clinic, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*6:00–9:30 p.m. Course in Child Psychiatry (Pediatric Neuropsychiatry). Metropolitan State Hospital, Waltham.
8:00 p.m. Norfolk District Medical Society. John Ware Hall, Boston Medical Library.

WEDNESDAY, NOVEMBER 26

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. (Childrens Medical Center.) Jimmy Fund Building, 25 Binney Street.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.
*4:00 p.m. Thoracic Conference. Held by Overholt Clinic, Harris Hall, New England Deaconess Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Neuropathology Conference. Drs. Adams and MacMahon. Pratt Diagnostic Clinic, New England Center Hospital.
*7:30 p.m. Lecture. Diseases of the Intestines. Drs. Richard B. Cattell and Everett O. Kiefer. Joslin Auditorium, Lahey Clinic.

*Open to the medical profession.